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OBSERVATIONS ON THE MODE OF ACTION OF SULFANILAMIDE AND ITS APPLICATION TO SURGICAL INFECTIONS

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THE DISCOVERY of the effectiveness of sulfanilamide in hemolytic Streptococcus infections has reopened the entire field of chemotherapy in bacterial diseases. It is now generally recognized that sulfanilamide therapy, properly conducted, will bring about a high percentage of cures in many types of invasive infection and septicemia which, until this drug was introduced, had been almost uniformly fatal. The surprising results of sulfanilamide therapy have created new problems for those interested in fundamental aspects of the control of bacterial invasion. The lessons which may be learned through an intensive study of the mechanism of sulfanilamide action may find widespread application to other chemotherapeutic problems. Further progress in this field is dependent upon a clearer understanding of the mechanisms by which the drug influences bacteria, and a more comprehensive knowledge of its toxic side-effects.

Since this new type of therapy has provided the surgeon with such an efficient weapon in the prevention and control of certain rapidly invasive infections, it is proper that laboratories of surgical research concern themselves with the fundamental problems which this new therapy has opened. Experiments which we have conducted in the Department of Surgical Research at the University of Pennsylvania offer, we believe, an answer to some of the perplexing problems which now confront us, and, in addition, provide a rational basis for the use of the drug.

Experimental Observations.—The fundamental observations of Marshall and of Colebrook, and their coworkers, are of the greatest importance to anyone interested in this field. Marshall[1] has demonstrated that sulfanilamide is quickly absorbed when administered either orally or parenterally, and becomes distributed with surprising uniformity throughout all the tissues and body fluids. It is rapidly excreted by the normal kidney, much of it in unaltered form. By repeated dosage of the drug, at short intervals, an equilibrium can be established in which the level of the drug in the blood and tissues remains fairly constant. These pharmacologic studies have supplied

the basis for the scheme of dosage now generally employed in practical therapy. The blood level of sulfanilamide must not drop below the therapeutically effective level until after the infection is controlled, or cured, if reactivation of infection is to be avoided. The optimum level for treatment of severe cases seems to lie between 5 and 10 mg. per 100 cc. of blood.

Colebrook,[2] by finding that concentrations of sulfanilamide in blood of between 5 and 10 mg. per cent provided the blood with a high capacity to kill Streptococci in vitro, made a significant contribution to the understanding of the mode of action of sulfanilamide. In his experiments it made no fundamental difference whether the sulfanilamide blood was obtained from a treated patient, or through the addition of the chemical to normal blood. Some time before the introduction of sulfanilamide, Hare[3] had discovered that recovery from severe hemolytic Streptococcus infection was always accompanied by a marked increase in the bactericidal titer of the blood against the organism. Thus Colebrook's observation that sulfanilamide induced a streptococcidal activity in blood could reasonably indicate that the absorption of the drug by the body tissues endowed them with resistance to Streptococcus infection similar in its effects to that occurring in the tissues of the patient convalescing from an active infection which had been overcome through natural immune processes.

Our studies were prompted by the hope that an understanding of the mechanism by which blood containing sulfanilamide kills Streptococci in the test tube might provide a basis for explaining the action of the drug against organisms in the tissues and circulating blood.

Technic.—We have made the effort to provide experimental conditions which would resemble tissue conditions during invasive infection as closely as possible. Hemolytic Streptococci of a virulent strain were grown for two hours in a medium containing 20 per cent of horse serum. This permitted testing the effect of the drug on young Streptococci in the encapsulated form, which Ward and Lyons[4] have shown to be the most highly resistant to the destructive action of phagocytes. Moreover, it is quite possible that these young organisms, grown in serum-rich medium, resemble more closely than older organisms the rapidly multiplying Streptococci which are active in invasive tissue infection. The Streptococci were separated from the horse-serum-peptone culture medium by centrifugation and resuspended in human serum before adding them to the test blood. This was done in order to avoid the addition with the organisms of traces of the original culture medium. Blood was freshly obtained from the same normal human subject for each experiment and defibrinated with glass beads. Mixtures of whole blood, or its serum, and sulfanilamide, 10 mg. per 100 cc., were prepared in small test tubes. For each tube containing sulfanilamide there was a corresponding control tube from which the drug was omitted, with all other experimental conditions identical. The Streptococci were then added in equal numbers to each of the tubes which were then sealed and rotated slowly on a mixing machine in the incubator at 37.5° C. At suitable intervals the tubes were

opened and, by making blood-agar pour plates of 0.1 cc. of the contents, determinations were made of the number of living organisms in each mixture.

Chart 1 is a logarithmically plotted representation of the population curves, which demonstrates the effect of sulfanilamide under experimental conditions *in vitro*.

Growth of Streptococci in Whole Blood.—The increase in population of hemolytic Streptococci in sulfanilamide-free whole blood proceeded rapidly from the start of incubation, so that in four hours there were about ten times as many organisms as at the beginning of the experiment. Smear studies at this time showed that active ingestion of many organisms by phagocytes had taken place, but phagocytosis under the conditions of the experiment was incapable of bringing about more than a transient reduction in the rate of multiplication. In 24 hours complete hemolysis of the blood had taken place and the bacterial population had increased to many millions. This level was

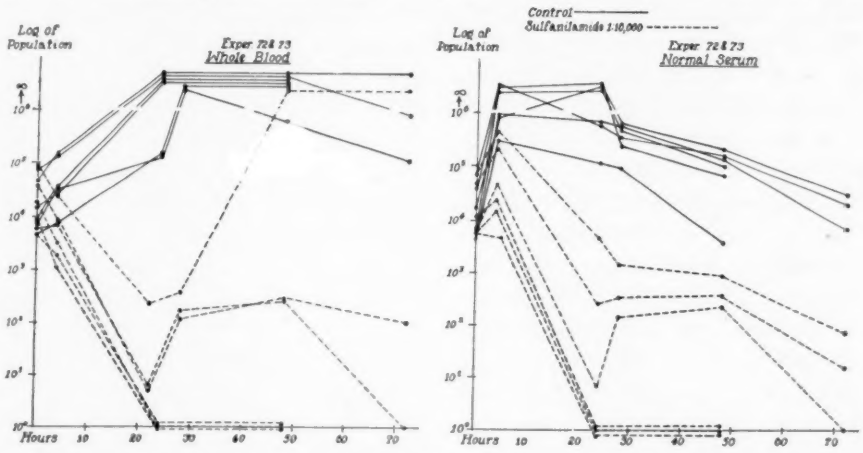

CHART 1.—Comparison of effect of sulfanilamide on Streptococci in whole blood and in serum. Logarithmic representation of bacterial population in 0.1 cc. at intervals indicated. Interruption of lines above Log 6.0 signifies growth to "infinity," *i.e.*, the number of colonies too great to count.

too high to permit direct counting of the colonies on the plates, even with the aid of the microscope.

When 10 mg. per 100 cc. of sulfanilamide was present, a rapid trend toward sterilization developed which was clearly defined even at four hours. Thereafter, the course of the population curve was related to the initial number of organisms implanted. The bloods containing the smallest starting population were sterile within 24 hours. The blood with the largest inoculation showed temporary reduction of the number of organisms, but sterilization did not occur. In fact, following the low point of population in this tube, which was at 24 hours, progressive outgrowth of organisms ensued. The blood became hemolyzed, and the final level of bacterial growth was identical with that in the sulfanilamide-free controls.

Discussion.—In considering the significance of this experiment it is apparent that the possibility that phagocytosis is an active participant in the

sterilizing action of sulfanilamide must be considered. The increased bactericidal action of the blood of convalescent patients has been generally believed to result from an increase in phagocytosis. One explanation of the bactericidal action of sulfanilamide in whole blood might be that the drug, by inducing a surface alteration in the organisms, increases their susceptibility to phagocytosis. One finds in the current literature that there is some indirect evidence which might tend to support the concept that sulfanilamide acts through promotion of phagocytosis. That this does not adequately explain the phenomenon is, however, evident when we find that normal serum, which contains no phagocytes, is just as effective a vehicle as whole blood for the action of sulfanilamide in destroying Streptococci.

Growth of Hemolytic Streptococci in Normal and Inactivated Serum.—In comparing the action of sulfanilamide in whole blood, and in serum, the following points deserve mention:

(1) More rapid initial outgrowth took place in sulfanilamide-free serum than in sulfanilamide-free whole blood. This was due in all probability to the absence of any phagocytes in the serum.

(2) The sulfanilamide-free serum failed to support a level of bacterial growth as high as the sulfanilamide-free blood. This has been related in other experiments to the lack of products of hemolysis in the serum. In whole blood, the breakdown of blood cells produced by streptococcal hemolysin enriches the medium to such a degree as to permit greater numbers of Streptococci to continue multiplying.

(3) Sulfanilamide in the serum allowed a temporary, but slight, increase in population during the first four hours. Following this initial phase of limited outgrowth, there was a progressive trend toward sterilization, similar to that which developed in the whole blood containing sulfanilamide.

Discussion.—The capacity of sulfanilamide to interfere with the multiplication and survival of hemolytic Streptococci in cell-free serum tends to rule out the mechanism of phagocytosis as a major essential participant in the action of the drug.

Normal serum, even without sulfanilamide, is not a suitable culture medium for *prolonged* survival of hemolytic Streptococci. This is shown in the controls by progressive reduction in the number of surviving organisms after 24 hours. The parallelism between curves obtained from the three sulfanilamide-containing tubes in which early sterilization did not take place, and the curves of the corresponding sulfanilamide-free controls, suggests that the effect of sulfanilamide might have been to exaggerate the inhibiting influence on streptococcal growth which is an attribute of normal serum. However, serum may be rendered much more suitable for prolonged multiplication and survival of Streptococci by the addition of small amounts of peptone. The major source of nitrogen in pure serum is the serum protein. The addition of peptone provides the bacteria with an additional, and more easily assimilable, source of nitrogen.

Bainbridge[5] has shown that some species of bacteria are unable to break

down protein molecules to obtain essential nitrogen, and literally "starve to death" in a medium of serum protein or egg albumin unless predigested protein, in the form of peptone, is supplied to them. Apparently the virulent hemolytic Streptococcus can utilize protein to some extent, as evidenced by the rapid initial growth in population of the organisms in normal serum. Supplementary experiments have shown us that nonvirulent Streptococci almost completely lack the ability to grow in peptone-free serum. Data which we obtained suggested the possibility that sulfanilamide may produce its restricting action on the growth of virulent Streptococci in serum by interfering with their utilization of serum protein. The following experiment offers indirect evidence on this important point.

Influence of Peptone on the Action of Sulfanilamide.—The population curves for hemolytic Streptococci in serum containing sulfanilamide were

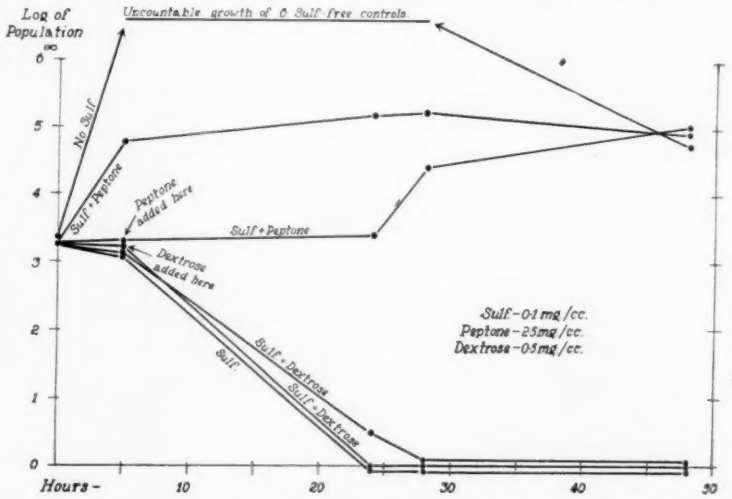

CHART 2.—The effect of peptone on the action of sulfanilamide. The uppermost curve is the average of the six sulfanilamide-free controls, the populations of which were at uncountable levels for most of the period of incubation.

calculated as in the preceding experiments. In addition, the growth curves were estimated for serum-sulfanilamide mixtures to which a small amount of peptone had been added. In one instance the peptone was added at the beginning of incubation, and in another it was introduced after five hours of incubation. As a further control, there was added to other tubes of serum a small amount of dextrose, which, like peptone, may under some conditions stimulate bacterial growth. Chart 2 shows the effects of these substances on the population curves.

(1) No population increase occurred during the first five hours in serum-sulfanilamide tubes which did not contain peptone. A marked increase in population took place when peptone was present. The addition of dextrose did not encourage growth.

(2) The addition of peptone after five hours of incubation of the culture permitted survival of the Streptococci and eventual increase of population

to the level of sulfanilamide-free controls. Failure to add peptone permitted the restricting effect of sulfanilamide to continue, and no living organisms remained after 24 hours.

Discussion.—In many experiments of a similar character, employing different types of peptone, the inhibiting effect of peptone on the action of sulfanilamide has been constantly apparent. We believe that this evidence justifies the tentative conclusion that sulfanilamide interferes with the ability of virulent hemolytic Streptococci to use serum or tissue protein as a "food" from which to obtain nitrogen. If no source of nitrogen other than protein is present in the bacterial environment, the organisms cannot continue to multiply and the population dies out.

We hope that through study of the enzyme actions by which invasive

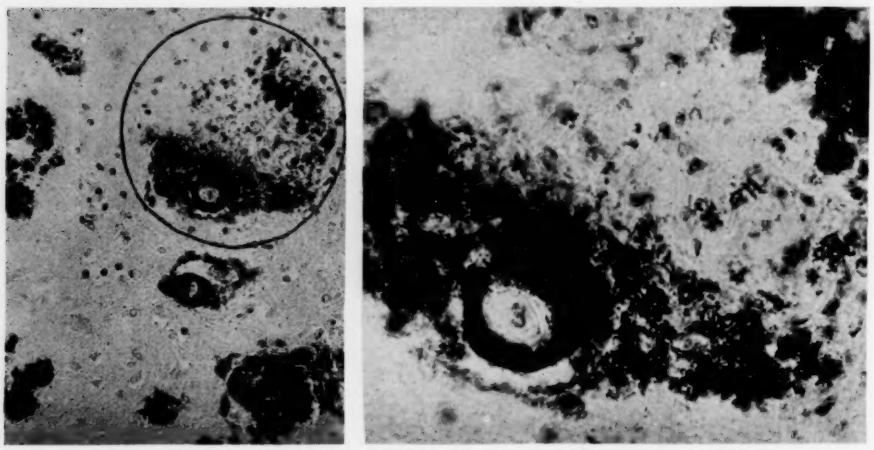

FIG. 1.—(A) Illustrates a highly invasive infection, and shows a photomicrograph of a section of the brain of rat dying 30 hours after introduction of hemolytic Streptococci into subarachnoid space through a cranial trephine. Note the grouping of masses of cocci around small vessels; complete absence of cellular exudate; and organisms spreading through tissues which are architecturally almost normal. (×400) (B) Higher magnification of (A) (circle). Note the cocci within a blood vessel; and absence of phagocytes. (×1,400)

organisms attack protein we may obtain direct evidence which will prove, or disprove, the validity of this concept. It has been of interest to us to note, however, that this explanation of the action of sulfanilamide conforms with the clinicopathologic alteration induced by sulfanilamide in infectious lesions in patients and animals.

The course of Streptococcus infection in over 200 patients treated with sulfanilamide last year at the Presbyterian Hospital in New York City was studied by Dr. Alvin Coburn and myself.[6] From this study it was concluded that the most striking effect of sulfanilamide was the suppression of tissue invasion in actively or potentially invasive infections. The patients with erysipelas, fulminating cellulitis, primary hemolytic Streptococcus peritonitis and meningitis were brought under control more rapidly and completely by sulfanilamide than the patients with the less virulent, more subacute

types of infections. The highly invasive Streptococcus lesions are characterized histologically by minimal changes in the tissue architecture at the peripheral zone of bacterial invasion. The organisms are actively multiplying in, and spreading through, tissues not yet digested by the action of inflammatory exudates[7] (Fig. 1A, B). In this type of process the organisms are apparently utilizing the proteins of the intact tissues for synthesis of their bacterial proteins, and in this type of lesion sulfanilamide acts with greatest effectiveness. Such a lesion may be compared to the infected normal serum of our experiments, the medium in which sulfanilamide has been shown to exercise a sterilizing action on Streptococci.

Furthermore, it appeared in our clinical study that the presence of necrotic tissue or pus in a lesion prevented sulfanilamide from acting upon the organisms with the same maximum effect which characterized its action on diffuse nonsuppurative infections. If an infection was treated after two or three days of progression, and some degree of localization or abscess formation had occurred, sulfanilamide seemed clinically to accomplish little more than to protect uninvolved tissues. Necrotizing tissue and pus contain peptone-like products of protein disintegration. It may be that the presence of this material in tissue lesions protects Streptococci from the full action of sulfanilamide through a mechanism similar to that which we have observed under experimental conditions. In the suppurative infections the bacterial environment is rich in peptones, the organisms are not dependent upon utilizing protein for survival, and are therefore able to resist the action of the drug.

CONCLUSIONS

(1) The sterilizing action of sulfanilamide under experimental conditions is not dependent upon the participation of phagocytic cells.

(2) Sulfanilamide in serum is capable of preventing the multiplication of hemolytic Streptococci.

(3) The sterilizing effect of sulfanilamide upon hemolytic Streptococci in serum is prevented by the addition of small amounts of peptone.

(4) Indirect evidence is offered to suggest that sulfanilamide acts upon hemolytic Streptococci by interference with their protein-digesting mechanism.

(5) Some of the clinical results of sulfanilamide therapy are explained through these concepts of the action of the drug.

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TOXIC MANIFESTATION OF SULFANILAMIDE*

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IT IS obvious that for the proper use of any therapeutic compound a knowledge of its possible harmful effects is necessary. This is especially true in regard to therapy with sulfanilamide because this chemotherapeutic agent, while possessing a low degree of acute toxicity for both man and animals,[1, 2, 3] is capable of producing a wide variety of undesirable side-effects in human beings.

We wish to discuss the toxic manifestations which have occurred during the course of sulfanilamide therapy in 335 patients at the Johns Hopkins Hospital, together with certain observations upon the recognition and control of such manifestations.

In our original report,[1] we noted the occurrence of certain cerebral toxic effects in mice and in human beings. These are among the most common toxic effects and consist of dizziness, headache, a loss of the ability to concentrate, a loss of normal reaction time, anorexia, nausea and, in some instances, vomiting. These manifestations by themselves have rarely been severe enough to warrant discontinuing the drug in ward patients but symptoms in this group are frequently very annoying to the ambulatory patient and may be severe enough to necessitate stopping the drug. It is of interest to note that sulfanilamide and alcohol tend to complement each other in their toxic effects, and because of this the use of alcohol should be discouraged in patients receiving sulfanilamide. The decreased mental acuity and dizziness which sometimes occur in the course of sulfanilamide therapy may render the ambulatory patient dangerous insofar as driving a motor vehicle is concerned. Professional motor vehicle drivers should be warned in this respect. Because of the frequency of these cerebral effects we feel that whenever it is practical the patient who is receiving sulfanilamide should be kept in bed—at least during the first days of treatment.

Cyanosis of varying degrees is almost a constant finding in patients treated with sulfanilamide. The mechanism of the production of the cyanosis is still in dispute. Marshall[4] does not believe that the formation of methemoglobin is always responsible for the cyanosis while Wendell[5] has stated that varying degrees of methemoglobinemia have been found in 200 patients treated with sulfanilamide. Despite certain dissident foreign observations,[6, 7, 8] the cyanosis does not seem to be due to sulphemoglobinemia. We have noted intense cyanosis appearing within four hours after the ingestion of 1.5 Gm. of sulfanilamide, and on the contrary we have noted patients in

* These investigations have been supported by a grant from the Chemical Foundation, Inc.

whom large doses (3.6 to 7.2 Gm. per diem) of sulfanilamide produced but mild degrees of cyanosis. We do not believe that the development of cyanosis, by itself, constitutes a dangerous toxic manifestation in the course of sulfanilamide therapy, nor do we believe that cyanosis is a contraindication to further treatment.

Clinical acidosis, as evidenced by the combination of hypernoia and a lowered CO_2 combining power, has been noted in 3 per cent of the 335 patients who comprise this study. As we have previously stated,[9] the acidosis is accompanied by loss of sodium and potassium in the urine. Since we have adopted the routine procedure of prescribing bicarbonate of soda with each dose of sulfanilamide, we have not noted this toxic manifestation. The amount of bicarbonate of soda needed to eliminate the possibility of acidosis is from one-third to one-half of the dose of sulfanilamide. If sulfanilamide is being given by the parenteral route, the use of one-sixth molar* sodium lactate solution as the solvent for the drug will prevent the occurrence of acidosis. If acidosis should occur, then the oral administration of sodium bicarbonate or the parenteral use of one-sixth molar* sodium lactate solution is indicated.

Jaundice (without anemia) accompanied by a marked decrease in liver function has occurred but once in this series of patients. The jaundice rapidly disappeared and the liver function returned to normal soon after sulfanilamide therapy was discontinued. We do not believe that the previous existence of liver damage or jaundice is necessarily a contraindication to sulfanilamide therapy. This is especially true if the existing liver damage is the result of an infection in which therapy with sulfanilamide is indicated.

We have not noted any evidence of renal damage or irritation which could be remotely attributed to sulfanilamide. It is to be remembered in this connection that the damaged kidney does not excrete sulfanilamide easily, and care should be taken that sulfanilamide does not accumulate in the blood stream in patients with impaired renal function.

Dermatitis has been relatively uncommon in this series of patients with but 1 per cent of the group showing this type of toxic reaction. This figure is lower than that observed by Hageman and Blake,[10] and by Schwentker.[11] In our experience the rash has always been similar to that of measles. All have been accompanied by some degree of temperature and all have cleared rapidly when the drug was discontinued. This procedure will do away with the possibility of a severe dermatitis of the exfoliative type developing. In one instance in which sulfanilamide was given again after the rash had disappeared, a mild dermatitis developed rather promptly. In but one case has the dermatitis seemed to be associated with a photosensitivity of the skin.

Simple fever has been the most common toxic reaction (6 per cent) noted in this series of patients. Frequently the question is asked as to how one differentiates the fever due to sulfanilamide from that due to the infection. It is interesting to note in this respect that in but one instance has this ques-

* *N.b.*, molar solution represents one containing 18.67 Gm. per liter.

tion had to be decided in the 22 patients in our series who developed fever as a toxic manifestation of sulfanilamide therapy. All of the other patients had had one or more days of normal temperature before they developed the drug fever.

The time of the occurrence of the fever is of interest. Two patients developed fever on the first day of therapy with sulfanilamide, four on the third day, one on the fourth day, two on the fifth day, two on the sixth day, four on the seventh day, two on the eighth day and five on from the ninth to the fourteenth day of treatment. Thus it is evident that fever may occur at any period in the course of sulfanilamide therapy.

In addition to simple fever due to sulfanilamide, we have noted that in almost all instances the patients developing a dermatitis, an acidosis, an acute hemolytic anemia or an agranulocytosis also show an early febrile response. Because of this, we have come to the conclusion that the appearance of fever constitutes an important warning sign in the control of patients being treated with sulfanilamide, and that sulfanilamide should be promptly discontinued in patients who develop an unexplained fever.

Inasmuch as simple fever is a fairly common toxic manifestation in the course of sulfanilamide therapy, the question of whether it is dangerous to resume treatment with the drug after the fever has disappeared is of importance. Our observations lead us to believe that it is impossible to predict whether a given patient will develop another febrile reaction if sulfanilamide therapy is resumed. However, because of the intensity and sharpness of the febrile reactions which have followed the restoration of sulfanilamide therapy in certain patients, we believe that it is wise to administer a test dose of 0.3 Gm. of the drug to patients who have previously had a febrile response to sulfanilamide. Then, if no febrile reaction occurs within 12 hours, it has seemed safe to continue with the drug. If, on the other hand, a sharp febrile response is noted, it is unwise to attempt further sulfanilamide therapy.

Anemias of the hemolytic type have occurred quite commonly in this series of patients. Fortunately, most of the anemias were mild in type and slow in developing. A drop in hemoglobin of from 10 to 20 per cent is a common finding in the course of sulfanilamide therapy, especially if the treatment is prolonged over a period of ten days or more. These slowly developing anemias are not accompanied by bilirubinemia, although increases in the reticulocyte count above normal limits are the rule after the hemoglobin begins to drop. Urobilin is almost constantly present. Our observations lead us to believe that these slowly developing mild anemias are not a contraindication to the continuation of sulfanilamide therapy.

Acute hemolytic anemias,[13, 14] characterized by a rapid fall in the red blood cell count and the hemoglobin, a moderate to a marked leukocytosis, marked reticulocytosis, bilirubinemia, urobilinuria and in certain instances porphyrinuria, have occurred in 3 per cent of the patients included in this series. This type of toxic manifestation is one of the most serious encountered in the course of sulfanilamide therapy. These anemias have generally been severe enough

to necessitate one or more transfusions. They occur within 24 to 72 hours after treatment has begun. The maximal anemia generally develops within three days after the hemolytic process is initiated. All of these patients show a definite rise in temperature during the anemia phase. This toxic manifestation is more common in children than in adults. In one instance in which therapy with sulfanilamide was resumed the hemolytic process recurred.

The mechanism of this type of anemia is not as yet clearly understood but it would seem to be the result of an individual idiosyncrasy toward sulfanilamide. There is no evidence that any one type of infection predisposes an individual toward this form of anemia. Experience has shown that sulfanilamide should be discontinued if an acute hemolytic anemia develops.

Agranulocytosis has been reported in the course of sulfanilamide therapy.[15, 16] We have noted one patient, suffering from a gonococcal arthritis and urethritis, who developed this toxic manifestation toward the end of the third week of treatment. This patient showed the typical picture of agranulocytic angina. Treatment designed to rid the patient of sulfanilamide was immediately instituted, and within ten days he had made a complete recovery from this blood dyscrasia. The mechanism of the production of serious leukopenias and agranulocytosis by sulfanilamide is as yet unknown.

Sulfanilamide is excreted by the kidneys, as has been shown by Marshall[17] *et al.* Therefore, when any type of toxic manifestations due to this drug occurs and it is desired to rid the organism of sulfanilamide as quickly as possible, large quantities of fluid should be given. The ensuing water diuresis will result in the rapid elimination of sulfanilamide from the blood and tissues.

CONCLUSIONS

Sulfanilamide produces many and varied toxic effects in human beings. However, we believe that if therapy with sulfanilamide is controlled by careful clinical and laboratory observations, the toxic manifestations of the drug will be recognized in their inception and no great harm will come to the patient. Detailed observations of the patient, careful temperature recordings and daily blood studies are exceedingly important in the care of the individual who is being treated with sulfanilamide.

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THE EFFECT OF SULFANILAMIDE UPON HUMAN, VIRULENT HEMOLYTIC STREPTOCOCCI

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IT IS a matter of easy confirmation that the addition of sulfanilamide to nutrient broth or human serum slows down the rate of multiplication but does not lead to the death of B-hemolytic Streptococci implanted in such media.[1, 4] This bacteriostatic influence cannot be said to constitute the sole mode of action of the drug because it is established that sulfanilamide enhances the bactericidal powers of human blood[2] in infected patients. The only known method whereby the body can destroy gram-positive Cocci is the process of phagocytosis and intracellular digestion. The effective action of sulfanilamide has been shown to depend upon the presence of phagocytic cells,[1] and it is reasonable to postulate that sulfanilamide has some action which renders this phagocytic mechanism more effective in killing hemolytic Streptococci. It is obvious, as observed by Reimann,[3] that this streptococcidal effect must be attributable to one or more of three possibilities: (1) A specific activation of the reticulo-endothelial system; (2) an inhibition of toxin formation; and (3) an alteration in the capsule of the Streptococcus. It is instructive to discuss the findings of other workers in relation to these possibilities.

(1) *Specific Activation of the Reticulo-Endothelial System.*—The reticulo-endothelial system may be considered to include the phagocytic cells and the specific antibodies of the serum. Sulfanilamide therapy does not alter the cytologic response to infection in experimental animals.[4, 5] There are no reported experiments which deal directly with antibody formation in sulfanilamide treated animals, but it is possible to evaluate this effect by a consideration of reported protection experiments. Mice survive the intraperitoneal injection of many lethal doses of Streptococci as long as sulfanilamide therapy is continued, but when the drug is withdrawn many of the animals subsequently die of their infection,[6] and it is, therefore, unlikely that sulfanilamide therapy has stimulated an active immunity during the time of treatment. Seastone[7] has demonstrated that the surviving guinea-pigs of sulfanilamide treated Group C-hemolytic Streptococcus infections are susceptible to reinfection. There is no evidence that antibody formation is specifically stimulated by sulfanilamide, and it may be concluded that the drug does not specifically activate the reticulo-endothelial system insofar as antibody production by that system is concerned.

(2) *Inhibition of Toxin Formation.*—Bliss and Long[1] have remarked

that toxin formation is probably suppressed by virtue of the bacteriostatic action of sulfanilamide to a point at which the Streptococci "no longer produce enough 'leukocidin' and other toxic products to inhibit rapid phagocytosis." Osgood and Brownlee[8] have observed that Streptococci grown in the presence of sulfanilamide produce less than normal quantities of hemolysin. From this it is argued that sulfanilamide inhibits the total toxigenic activity of Streptococci and thereby converts the organisms to "harmless saprophytes." The experimental evidence available at the present time does not appear to us to be sufficient to conclude that such an inhibition of toxin formation could be the adjuvant factor supplied by sulfanilamide in the bactericidal mechanism observed in the clinical use of the drug.

(3) *Alteration of the Capsule.*—Levaditi and Vaisman[11] advanced the hypothesis that the action of the drug might be attributable to an inhibition of encapsulation. This viewpoint was not tenable after the demonstration of encapsulated organisms in the peritoneal cavities of treated mice,[12] but distinct degenerative changes have been observed in the morphologic appearance of Streptococci grown in sulfanilamide serum.[4] Bliss and Long[1] have shown that the Streptococci in the peritoneal cavities of infected mice are more readily phagocyted in sulfanilamide treated animals than in normal controls. This increased phagocytosis in the absence of specific antibacterial antibody is evidence of an alteration in the surface or capsular antigen.[9, 10] The truth of this is not denied by the histologic demonstration of a capsule because it is immunologically possible to differentiate between two types of morphologically identical capsules.[9, 10] Hemolytic Streptococci in the human virulent phase are encapsulated and resistant to phagocytosis, whereas variants of attenuated virulence may be encapsulated and susceptible to phagocytosis. The failure of active immunization to occur in sulfanilamide treated animals is consistent with an antigenic alteration in the structure of the bacteria.

In the present report we wish to present the experimental data which demonstrate that there is a physicochemical alteration of the structure of B-hemolytic Streptococci grown in the presence of sulfanilamide. It was elected to perform these studies in human blood because there are many discrepancies between the infections in humans and those in mice. The F variant of the hemolytic Streptococcus is virulent for man but has little or no primary virulence for mice.[9, 10] Sulfanilamide therapy does not protect mice infected with freshly isolated human strains or strains of low mouse virulence.[5, 6, 12] The drug appears to have little or no effect on the established mouse infection,[5, 6, 13, 14] whereas, it is only applicable to humans with preexistent infections. The bactericidal effect of sulfanilamide is demonstrable in human blood but not in the blood of lower animals,[2, 12] but this is probably due to the lesser phagocytic efficiency of the circulating leukocytes of these animals.

Experimental Methods.—(1) *Source of B-Hemolytic Streptococci.*—The bacteria were obtained from blood cultures and direct platings of pus from human lesions. The strains were studied at the time of isolation to determine

whether one or more variants were present. Stock cultures were grown overnight in a meat tube, covered with mineral oil and stored in the refrigerator.

(2) *Cultivation.*—The composition of differential blood agar plates and serum neopeptone water has been reported.[9, 10] Sulfanilamide (Merck) has been added as dried powder to a concentration of 10 mg. per cent prior to autoclaving, and desired dilutions in neopeptone water prepared.

(3) *Spontaneous Agglutination.*—This technic has been reported.[9] Equal quantities of overnight culture and saline are placed in the water bath at 55° C. for three hours, and read with the naked eye for agglutination.

(4) *Phagocytosis.*—The complete details of this technic have been reported.[9] The resistance to phagocytosis of virulent variants was checked in every experiment by the use of infant blood or washed adult cells resuspended in a 1:8 dilution of homologous serum in saline.[9, 10] Sulfanilamide blood was obtained directly from patients receiving the drug or was prepared by adding sulfanilamide (Merck) to freshly drawn, defibrinated blood.

(5) *Bactericidal Technic.*—These tests were performed by the modified Todd technic.[16] Sixteen-hour cultures were serially dilulted in homologous media without horse serum and added to tubes of the defibrinated blood. The tubes were sealed, rotated for 48 hours at 37° C. and then cultured upright for 24 hours at 37° C. The contents of each tube were then washed into 5 cc. of 5 per cent horse serum neopeptone water and incubated at 37° C. overnight. Smears and cultures were made of these last named cultures to determine which of the bactericidal tubes contained bacteria.

(6) *Sulfanilamide Determinations.*—The sulfanilamide levels of the blood and media were determined by the method of Marshall.[17]

(7) P_H *Determinations.*—These observations were performed with the colorimetric method and checked by the electrometric technic.

Experimental Results.—(1) *Variation in Form of Colonies.*—Gay and Clark[4] observed that Streptococci grown in human serum containing sulfanilamide and then transplanted onto differential media gave rise to a mixture of virulent and avirulent colony forms on primary subculture which reverted to all virulent colony forms on subsequent subculture. This observation was confirmed and it was further found that normally grown Streptococci transplanted onto differential media containing 10 mg. per cent of sulfanilamide also yielded a mixture of virulent and avirulent colony forms. Sulfanilamide-grown Streptococci transplanted onto sulfanilamide media produced all avirulent colony forms but subcultivation back onto normal media resulted in a reversion to the virulent colony form.

(2) *Spontaneous Agglutination.*—The capsules of the virulent M and the attenuated M variants are morphologically identical, but the virulent variants are resistant to phagocytosis in the absence of specific antibacterial antibody and do not agglutinate spontaneously, whereas the attenuated variants are readily phagocyted and are spontaneously agglutinable.[9, 10]

Table I shows the results obtained from an experiment in which virulent strains are rendered spontaneously agglutinable by progressive subcultivation

in sulfanilamide media. Similar experiments, with many strains, have shown a great variation in strain susceptibility to this sulfanilamide-induced spontaneous agglutination, but practically all strains show some agglutination after three subcultures in 10 mg. per cent sulfanilamide media. This agglutinability is attributable to an alteration in the structure of the organisms, because Streptococci which have been washed and resuspended in saline after growth in sulfanilamide media are similarly agglutinable and no alteration in P_H has been observed in the media used for these tests. The capacity for spontaneous agglutination is lost in the first normal subculture away from sulfanilamide media. It is concluded that continued growth in sulfanilamide media conditions a physicochemical alteration in the surface antigen of B-hemolytic Streptococci. It has been impossible to determine whether this change is due to an absorption of some substance onto the Cocci or to a direct modification of the capsule.

TABLE I

THE SPONTANEOUS AGGLUTINATION OF STRAINS PASSAGED IN SULFANILAMIDE MEDIA

Amount of Sulfanilamide in Media	Subculture					
	Strain "Gal."			Strain "Ber."		
	1st	2nd	3rd	1st	2nd	3rd
0 mg. %	0	0	0	0	0	0
2.5 mg. %	0	±	++	0	0	++++
5 mg. %	0	0	++	0	++	++++
10 mg. %	0	±	++	0	++	++++

TABLE II

THE PHAGOCYTOSIS IN AN INFANT'S BLOOD OF STRAIN "MCL" PASSAGED IN SULFANILAMIDE

History of Culture Tested	Normal Blood	Sulf.† Blood
33x in normal serum neopeptone	0 — 0%*	0 — 0%
32x in normal serum neopeptone, then 1x in sulf.† serum neopeptone	0 — 0%	0 — 0%
3x in sulf. serum neopeptone	90 — 18%	64 — 16%
33x in sulf. serum neopeptone	121 — 36%	160 — 34%
32x in sulf. serum neopeptone, then 1x in normal serum neopeptone	0 — 0%	0 — 0%

* 0 — 0% = 0 Streptococci phagocyted by 0 per cent of 50 cells counted.

† Concentration of sulfanilamide used in blood and media = 10 mg. per cent.

(3) *Phagocytosis.*—Table II shows the results obtained from a phagocytic experiment with infant's blood containing no demonstrable antibacterial antibody to Streptococci. It is shown that progressive subcultivation in sulfanilamide media renders the organisms susceptible to phagocytosis even in the absence of specific antibody, and that the bacteria revert to the phagocyte resistant form when they are subcultured into normal media.

TABLE III

THE EFFECT OF ANTIBACTERIAL ANTIBODY AND PASSAGE IN SULFANILAMIDE UPON PHAGOCYTOSIS IN ADULT BLOOD

Strain	History of Culture Tested	Normal Blood	Sulfanilamide* Blood
"McL"	1x in normal serum neopeptone.....	0 — 0%†	0 — 0%
	1x in sulf.* serum neopeptone.....	0 — 0%	0 — 0%
"Aps"	1x in normal serum neopeptone.....	112 — 36%	506 — 88%
	1x in sulf. serum neopeptone.....	334 — 54%	420 — 82%
"Gal"	1x in normal serum neopeptone.....	306 — 50%	592 — 72%
	1x in sulf. serum neopeptone.....	372 — 62%	701 — 78%

* Sulfanilamide concentration = 10 mg. per cent.

† Fifty cells counted.

(The blood used in this experiment contained antibody for strains "Aps" and "Gal" but not for strain "McL"; *c.f.*, the phagocytosis by normal blood of the normally grown strains.)

Table III shows that phagocytosis is most marked when Streptococci are grown in sulfanilamide media and are added to blood which contains both sulfanilamide and antibacterial antibody. This experiment also illustrates the variation of strains in their susceptibility to sulfanilamide.

TABLE IV

THE PROGRESSIVE ATTENUATION OF BACTERIAL VIRULENCE BY SUBCULTIVATION IN SULFANILAMIDE MEDIA

Phagocytosis*	Blood Sulfanilamide	History of Inoculum	Bacteria Killed by 0.25 Cc. Blood
0 — 0%	0 mg. %	15x in normal serum neopeptone	0
	10 mg. %	1x in sulf.† serum neopeptone	40
	10 mg. %	3x in sulf. serum neopeptone	300
	10 mg. %	5x in sulf. serum neopeptone	3,000
	10 mg. %	15x in sulf. serum neopeptone	6,000
	0 mg. %	14x in sulf. serum neopeptone, then 1x in normal serum neopeptone	0

* Twenty-five cells counted. This blood contains no demonstrable antibody for the test strain.

† Sulfanilamide concentration of 10 mg. per cent.

(4) *Bactericidal Tests.*—Table IV shows the results obtained from an experiment in which it is demonstrated that sulfanilamide grown organisms are killed by defibrinated human blood which contains no demonstrable antibacterial antibody. This bactericidal effect is shown to be due to an attenuation of bacterial virulence by sulfanilamide, because the only variable in the experiment is the progressive subcultivation of the Streptococci in sulfanilamide media, and the bacteria from the fifth subculture are killed in significantly larger numbers than the organisms from the first subculture. This effect of sulfanilamide also disappears as soon as the bacteria are cultivated in normal media again.

TABLE V

THE DEMONSTRATION OF THE NECESSITY FOR BOTH ANTIBACTERIAL ANTIBODY AND SULFANILAMIDE FOR THE MAXIMAL BACTERICIDAL EFFECT

Exper. No.	Phagocytosis*	Blood Sulf.	History of Inoculum	Bacteria Killed by 0.25 Cc.
1	0 — 0%	0 mg. %	3x in normal serum neopeptone	5
		10 mg. %	3x in sulf.† serum neopeptone	300
	124 — 60%	0 mg. %	3x in normal serum neopeptone	50
		10 mg. %	3x in sulf. serum neopeptone	30,000
2	0 — 0%	0 mg. %	3x in normal serum neopeptone	0
		5 mg. %	3x in sulf. serum neopeptone	1,300
	168 — 76%	5 mg. %	3x in sulf. serum neopeptone	130,000
3	210 — 88%	0 mg. %	3x in normal serum neopeptone	13
		10 mg. %	3x in sulf. serum neopeptone	30,000

* Twenty-five cells counted.

† Sulfanilamide concentration of 10 mg. per cent.

Table V shows the results obtained from a series of experiments which demonstrate that the combined action of sulfanilamide and antibacterial antibody is more effective than either one alone. Other similar experiments indicate that the effective level of antibody action is markedly lowered in the presence of sulfanilamide.

Experiments performed in human serum have failed to demonstrate any increase in the streptococcidal power of the serum as a result of the addition of sulfanilamide or the use of sulfanilamide-grown organisms. It is concluded that sulfanilamide affects the Streptococci to render them more susceptible to the bactericidal action of defibrinated whole blood.

(5) *Clinical Observations.*—A dramatic therapeutic response to sulfanilamide has occurred in the treatment of two types of acute hemolytic Streptococcus infections. The first type comprises those infections in which the patients have antibacterial antibody to their organisms at the time treatment is started; and the second type consists of those patients who have no antibacterial antibody and negative blood cultures with beginning localization of their infection by the process of inflammatory fixation. However, there is a third type of infection, in which the patient has a bacteriemia with no antibacterial antibody, and sulfanilamide therapy alone has failed to sterilize the blood stream in these cases.

There are six cases of bacteriemia without antibacterial antibody which have received sulfanilamide in sufficient dosage over a long enough period of time to evaluate adequately the sulfanilamide response in this type of infection. Three of these six patients died with continuously positive blood cultures on the second, third and fifth days, respectively, after sulfanilamide therapy was started. A fourth patient received only sulfanilamide and eventually recovered, but it was not apparent that the drug had dramatically influenced the course of his disease. The two remaining patients received sulfanilamide with no apparent improvement in the course of their bacteriemia. Sterilization of the blood stream and subsequent recovery followed

immediately upon the injection of antibacterial antibody by the method of immunotransfusion.[15]

TABLE VI

THE DEMONSTRATION OF THE RESISTANCE OF A STRAIN OF STREPTOCOCCUS TO THE EFFECT OF SULFANILAMIDE

Exper. No.	Phagocytosis*	Blood Sulf.	History of Inoculum	Bacteria Killed by 0.25 Cc.
1	0 — 0%	0 mg. %	3x in normal serum neopeptone	5
		10 mg. %	3x in sulf.† serum neopeptone	2
2	168 — 88%	0 mg. %	3x in normal serum neopeptone	500
		10 mg. %	3x in sulf. serum neopeptone	2,000

* Twenty-five cells counted.
† Sulphanilamide concentration of 10 mg. per cent.

Table VI shows the result obtained from a bactericidal experiment, with a strain of Streptococcus isolated from a patient who died with Streptococcus bacteriemia, despite the fact that a blood sulfanilamide level of 9 mg. per cent was maintained for three days prior to death. The experiment confirms the clinical observation that this strain of Streptococcus was relatively little affected by sulfanilamide and that antibacterial antibody was needed to achieve the streptococcidal effect. Tables VII and VIII are clinical summaries of the two patients with bacteriemia and no antibacterial antibody who required antibody in addition to sulfanilamide to sterilize the blood stream.

TABLE VII

CLINICAL SUMMARY OF A MALE, AGE 7, SUFFERING FROM BACTERIEMIA (STRAIN "MCL") WHO HAD NO ANTIBACTERIAL ANTIBODY, AND WHO REQUIRED ANTIBODY IN ADDITION TO SULFANILAMIDE TO EFFECT STERILIZATION

Days	Sulfanilamide Dosage	Sulfanilamide Blood Level	Transfusions	Blood Cultures	Remarks	W.B.C.
1	2.4			Pos.	Stuporous	5,000
2	2.4				Stuporous	
3	2.4				Stuporous	
4	2.4	7.7	Nonimmune 300 cc.*		Stuporous	6,000
5	2.4			Pos.	Stuporous	8,900
6	2.4				Stuporous	9,100
7	2.4	6.5		Pos.	Stuporous	10,400
8	2.4	4.9	Immune 350 cc.†		Stuporous	
9	2.4			Neg.	Reactive	15,500
10	2.4				First abscess	21,200

* Phagocytic titer : 0 — 0% (25 cells counted).
† Phagocytic titer : 175 — 68% (25 cells counted).

COMMENT.—Human virulent variants of hemolytic Streptococci are known to be resistant to spontaneous agglutination; resistant to phagocytosis; and resistant to the bactericidal power of human blood which contains no specific antibody.[9, 10] Streptococci which have been grown in media containing sulfanilamide have been shown to be spontaneously agglutinable; sus-

ceptible to phagocytosis; and killed by human blood that contains no specific antibody. These are the characteristics which serve to identify the attenuated or avirulent variants.[9, 10] Growth in sulfanilamide induces a physico-chemical alteration in the antigenic structure of hemolytic Streptococci which decreases the invasive capacity, or virulence, of the bacteria. These changes are strictly conditioned by the presence of the drug and are reversible upon withdrawal.

TABLE VIII

CLINICAL SUMMARY OF A FEMALE, AGE 20, SUFFERING FROM BACTERIEMIA, WHO HAD NO ANTIBACTERIAL ANTIBODY, AND WHO REQUIRED ANTIBODY IN ADDITION TO SULFANILAMIDE TO EFFECT STERILIZATION

Days	Sulfanilamide Dosage	Sulfanilamide Blood Level	Transfusions	Blood Cultures	Remarks
1	*			Pos.	T. 104° F., P. 140
2	0.4				
3	6.0	11.0			Irrational
4	6.3	6.9	Nonimmune 350 cc.†	Pos.	T. 103° F., P. 120
5	6.3	10.9	Immune 500 cc.‡	Pos.	
6	7.0	5.9	Immune Serum 260 cc.	Neg.	
7	0			Neg.	T. 99° F., P. 110
8	0				
9	0				T. 98.6° F., P. 80

* Patient received 40 cc. "prontosil" and was then changed to sulfanilamide by mouth.
† Phagocytic titer : 0 — 0% (25 cells counted).
‡ Phagocytic titer : 236 — 88% (25 cells counted).

Different strains of Streptococci vary in their susceptibility to this effect of sulfanilamide. Some strains are so altered by the drug that normal blood is bactericidal for these strains even in the absence of specific antibody. Other strains are affected so slightly that the bactericidal mechanism still depends upon the presence of antibacterial antibody for the streptococcidal effect, but it is believed that the efficiency of the antibody is increased for organisms of this type which have been grown in sulfanilamide.

It has been found that patients with sustained bacteriemias and no antibacterial antibody are inadequately treated by the use of sulfanilamide alone. The experimental and clinical evidence indicates that effective therapy for this type of infection should consist of sulfanilamide and the intravenous injection of specific antibacterial antibody by the immunotransfusion technic.

CONCLUSIONS

(1) Sulfanilamide has been found to render human virulent strains of hemolytic Streptococci more susceptible to the bactericidal action of human blood, and this effect is reversible upon withdrawal of the drug.

(2) Antibacterial antibody is necessary in addition to sulfanilamide in the treatment of certain types of sustained hemolytic streptococcal bacteriemias.

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DISCUSSION OF THE PAPERS OF DOCTORS LOCKWOOD, LONG AND BLISS, AND LYONS

DR. DEAN LEWIS (Baltimore, Md.): I am not a therapeutic optimist. When Doctor Long began his experimental work with this drug, I waited rather anxiously for a case which would be a true test of the therapeutic efficacy of the drug. I should ask Doctor McFee to say something about this case, for he may believe that the results would justify me in becoming a therapeutic optimist.

The patient was operated upon in 1930. He had an otitis media, and subsequently a mastoidectomy was performed. Chills and fever developed and the jugular vein was ligated became of thrombosis. Pain developed in the right hip. Blood cultures revealed a beta-hemolytic Streptococcus. It is not necessary to give a detailed history. In 1931, a suppurative arthritis of the right sacro-iliac joint developed. An abscess was opened and 150 cc. of thick pus removed. No rough bone was felt. In 1931, the patient was discharged from the hospital with a sinus. Subsequently the right sacro-iliac joint was drained, the right wing of the ilium was removed, and a diagnosis of a chronic suppurative arthritis of the sacro-iliac joint made. He did not improve rapidly and was sent to Rollier's clinic in Switzerland. In 1936, an abscess beneath the right iliac muscle was drained. Abscesses were also drained which were located in the deep muscles of the back. After this long clinical course he came to the Johns Hopkins Hospital. The Proteus organism and a Streptococcus were found. Forty-eight hours after the first dose of sulfanilamide, the temperature became normal. The character of the discharge from the 15 discharging sinuses changed and became thin and pink in color. Within six months the boy had gained 62 pounds and the discharging sinuses had healed. The patient has gone to a boys' camp in New Hampshire, and Doctor McFee told me this morning that the boy is now in New Orleans. About all there is to remind one of his serious illness is a peculiar Charlie Chaplin-like walk. This case furnishes a true test of the efficacy of this drug. Ever since, I have been looking for a case of Streptococcic osteomyelitis, such as that which occurs in children and often runs the clinical course of suppurative arthritis, for I am quite certain that the clinical course would be modified by the drug; and it is quite possible that if a sequestrum

formed, it could be sterilized, and that the sequestrum would then behave as a bone transplant.

Dr. Richard H. Miller (Boston, Mass.): As one may infer from what Doctor Lyons has said, we believe that the effect of the sulfanilamide is not dependent on any stimulation of the reticulo-endothelial system, or to any depreciation of toxin formation, but more probably to an alteration in the characteristics of the capsule of the Streptococcus.

Furthermore, it seems to us that the effect of sulfanilamide is variable, depending on the blood culture and also depending on the presence, in some instances, of an anti-bacterial antibody. Certainly, Doctor Lyons has been dramatically successful in saving some cases by employing blood transfusions in addition to sulfanilamide.

One more minor practical point may be spread by you to professional colleagues in consultations and conversations. That is, they must not allow themselves to have a false idea of security because they are employing sulfanilamide. All the ordinary measures of surgery, in addition to the use of this drug, must be used.

I should like to add one other point which brings me, I am afraid, into a little disagreement with Doctor Long, because I was going to say that we are quite against the use of sulfanilamide in any ambulatory cases. I had it in my mind to say that we would not advocate its use except in hospitalized patients, where we could make, at the necessary intervals, the proper blood examinations, determination of the red and white count, and, if necessary, the condition of the phagocytes and perhaps the blood level of the sulfanilamide itself.

Dr. Evarts A. Graham (St. Louis, Mo.): There are just two points that I should like to comment upon in regard to this symposium.

One is that I think perhaps all of the emphasis should not be placed on the therapeutic value of sulfanilamide. If we will recall the first experiments made with this drug by Domagk, we will recall that he found that this agent was much more effective in the prevention of Streptococcus peritonitis than it was in the cure of the disease after it had been produced.

As practical surgeons, I think that this point deserves a considerable amount of emphasis and so I am driving it home, if necessary. For several months now, we have been using it at the Barnes Hospital almost as a routine in cases in which we might have occasion to predict a flare-up of a streptococcal infection by operation. We have used sulfanilamide as a prophylactic measure beginning two days before the operation.

I have had the opportunity to observe what seemed to me rather striking results in the fact that in a considerable number of cases of chronic empyema, in which it was necessary to perform rather an extensive operation, with large incisions, going in the neighborhood of or passing through a sinus of the chest, already infected, it was possible by the use of sulfanilamide as a prophylactic measure to have these wounds healed by primary intention. Again, I have seen this same event occur in other parts of the body where it was probable that a severe streptococcal infection would take place as the result of an operation opening into an already infected field. It would seem to me that this principle might have a bearing upon problems which confront neurologic surgeons in brain abscesses; often and perhaps to an even greater extent, a bearing upon many of the problems which the gynecologist faces or the obstetrician, if you will, in dealing with latent infections of the pelvis in which subsequent operations are necessarily performed. We think we have

noted much better healing after intrathoracic operations, other than chronic empyemas, as the result of the prophylactic use of this agent, notably, for instance, in lobectomies.

The dose has been something which has bothered us. I don't know whether any of the speakers this afternoon would be able to enlighten us on what might be regarded as a suitable prophylactic dose. We have tried empirically several doses and several methods of administration. Now we ordinarily, because of our ignorance and lack of knowing what might be best, give the drug in a ratio of a twentieth of a gram per kilogram of body weight parenterally, and we give about 500 cc. slowly, subcutaneously, to the patient while he is on the operating table. We begin the administration of the drug preferably about two days before the operation and we continue it particularly while the patient is on the operating table.

There is just one other point I wish to mention and then I am through. Until last summer, I had never had the good fortune to see a patient with an acute suppurative pylephlebitis following an acute appendicitis recover. Others, of course, have seen such patients recover but I have never had that good fortune. It happened, however, that inside of six weeks, two patients developed this condition in the Barnes Hospital, both of them with jaundice, both of them with chills and high fever. In desperation, we thought we would take a chance on sulfanilamide. I couldn't be very optimistic about it but, at any rate, we used sulfanilamide on these two patients and they both made a rapid and uneventful recovery.

Dr. Allen O. Whipple (New York, N. Y.): I wish to pay tribute, to Doctor Lockwood for the work that he has been carrying on during the last two years, and I would like to say that he illustrates the possibilities of a resident contributing fundamentally and soundly to scientific work and at the same time developing into an excellent surgeon. I also would like to emphasize the importance of an adequately supervised bacteriologic laboratory working in the surgical department, headed by a man who understands both surgery and bacteriology.

I think Doctor Meleney deserves a great deal of credit for the stimulus he has given, not only to us at the College of Physicians and Surgeons, but to the other clinicians in advancing this type of work.

As an example of the teamwork that can be developed: Doctor Lockwood was one of a committee, at the Presbyterian Hospital, which supervised and reviewed all of the cases in which the administration of sulfanilamide was advised. The patient was not given sulfanilamide until one or more members of that committee had seen the case and advised its employment. As a result of that, a great deal of the helter-skelter and hit-or-miss therapy that has been carried out in a good many places with sulfanilamide was, I think, avoided.

This is a drug that carries with it possibilities for harm as well as for good, and in large hospitals, particularly, the work should be carefully supervised by both the medical and the surgical and the laboratory groups.

Dr. J. Shelton Horsley (Richmond, Va.): I would like to refer to a cure by sulfanilamide of a case of Streptococcic peritonitis by Dr. John S. Horsley, Jr. The diagnosis was apparently appendicitis, but at operation the appendix appeared grossly normal. There was a large amount of free, turbid fluid which contained Streptococci and other evidences of peritonitis. The case was treated with sulfanilamide and the recovery was dramatic.

As regards preparatory treatment, sulfanilamide is apparently not directly

bactericidal, but it seems to affect the capsule of the bacteria, rendering them more vulnerable to the phagocytes. In the Colibactragen of Steinberg, we have an excellent preparation for the prevention of peritonitis. Undoubtedly, it has a great deal of merit, and as Steinberg has shown, it is, of course, not a bactericidal preparation but it increases the number of phagocytes, and stimulates their activity and their effectiveness. If this Colibactragen is used in established peritonitis, it has no effect. The toxins of peritonitis seem to depress the phagocytes after peritonitis has been established. Sulfanilamide in some way seems beneficial both as a preventive and as a curative agent.

Dr. Vernon C. David (Chicago, Ill.): As far as I know, there has been no suggestion made that virus diseases may be beneficially influenced by sulfanilamide. I would like to report several experiences, in principle, that seemed to indicate that there are some beneficial effects from the use of sulfanilamide in lymphogranuloma inguinale. Any of you who have had experience with the treatment of that disease know that it is highly resistant to treatment of any type that we know of.

A few months ago, I saw a patient who had a very well developed rectal infection with lymphogranuloma inguinale, and for whom all the known methods of treatment had been employed, such as ammonium and potassium tartrate, the luetic treatment, *etc.*, none of which had resulted in any improvement.

Doctor Knight, of Chicago, suggested, after the failure of any therapeutic benefit from any of these methods, that we might try sulfanilamide. "Well," I said, "I think it's all right to use," and promptly forgot about it. About two months later, a doctor from the town in which this man lived wrote me and said that he had examined the patient, whom I had advised to have a colostomy performed for a lymphogranulomatous infection of his rectum, who, as far as he could discover by examination, was well. At my request the patient returned, and on examination showed very little evidence of the disease.

Now, that would be only suggestive, but at that time we had in the hospital a boy with a deep, progressive infection of the ischiorectal fossa which had involved the adductor region and which was accompanied by a secondary hemorrhage, for whom deep roentgenotherapy, tartar emetic and antiluetic treatment, treatment Frei antigen and everything else had been administered that we could think of, without any result whatsoever. Biopsy showed no carcinoma or tuberculosis. The Frei test was positive.

We therefore started this boy on sulfanilamide, giving him 20 gr., increasing it 20 gr. a day until he had 90 gr. a day for three days; then allowing him to rest for two or three days, and repeated this regimen seven different times. He immediately started to improve, and I had the pleasure of showing him to some of the men in this audience the other day; he is, apparently, entirely well.

Coincidentally with that, there have been about three or four other patients who have been treated the same way and all had evidenced marked improvement. I would suggest, in these very intractable cases and in the rather hopeless situation in instances of lymphogranuloma inguinale, it might be worth while to try this drug.

Dr. David E. Robertson (Toronto, Canada): The use of sulfanilamide has become world wide, and one reads nothing but good results from its administration. There is no denying the fact that following its administration there have been brilliant and picturesque recoveries made. It is equally true

that the drug is apparently wholly ineffective in other cases, even in instances where a high level of concentration is maintained in the blood.

One must remember that before the use or the knowledge of this drug existed, spontaneous recoveries did occur in streptococcal infections. I consider the drug is an agent that may be of the greatest use in the treatment of certain streptococcal and other infections, but it would be interesting to see a record in those cases in which it has failed to change the course of the disease.

DR. ERWIN R. SCHMIDT (Madison, Wis.): I would like to call attention to one phase of this subject: At our hospital, our anesthetists are extremely reluctant to put any people asleep who have had sulfanilamide and have had cyanosis.

They have a certain degree of anoxemia and in these cases where you have a short operation to perform, if you give them light anesthesia, such as nitrous oxide and oxygen, the chance for producing and increasing anoxemia is very definite.

DR. ARTHUR M. SHIPLEY (Baltimore, Md.): I would like to report one experience that has not been touched upon: The patient had a very active, localized pelvic inflammatory disease. I attempted to effect vaginal drainage. A short incision had only been made through the mucous membrane of the vaginal wall, when an alarming hemorrhage was encountered, which it took me three-quarters of an hour to control. I actually had to split the entire posterior vaginal wall. She was very cyanotic and the anesthetist was very much concerned during the whole procedure, although she was not half as frightened as I was. However, the patient recovered from the cyanosis, hemorrhage, operation and anesthetic.

The collection of pus, however, increased in the pelvis, so that later, it could be approached through a left McBurney incision. Her cyanosis had disappeared at the time of the second operation, and she had no unusual bleeding. The operation and drainage were accomplished without difficulty.

The relationship of intractable bleeding to the cyanosis, incident to the administration of sulfanilamide, has not been touched upon today and I would like to call attention to it.

DR. RALPH R. MELLON (Pittsburgh, Pa.): I should like to inquire of Doctor Lyons relative to what he said about the mechanism or action of the drug, namely, acting on the organism and so altering the surface capsule as to permit it to become phagocytic. If that really is an adequate explanation of the mechansim, why is it that Levaditi and others have shown that if the drug is injected directly into the peritoneal cavity of mice, these mice are not saved, but if it is injected subcutaneously or orally, the mice are saved?

Furthermore, why is it possible, if this mechanism is correct, to add the drug in high concentrations to Streptococci in the test tube and then, the mice, being injected with these organisms, are still not saved even though premobilization of the phagocytes have been brought about?

DR. JOHN S. LOCKWOOD (closing): As far as the practical application of sulfanilamide therapy in surgical infections is concerned, our own experience has been quite similar to that of Doctor Long, and I am inclined to subscribe to the principles that he presented so clearly. We have not used the very large initial doses which he recommends but there is certainly a good deal of rationale in so using the drug.

I do not think we will attempt, on this occasion, to unravel the differences

of opinion on the action of sulfanilamide which have been promulgated. Perhaps it is not surprising that there should be almost as many differences in the understanding of the action of the drug as there are people working with this material.

There are certain points, however, that I would like to bring up with respect to the situations in which the action of the drug is limited. We had a baby of 11 months with a primary Streptococcic peritonitis, who was treated with sulfanilamide and whose peritonitis cleared up very dramatically. However, during the course of intensive sulfanilamide therapy, this child developed a suppurative phlebitis of the saphenous vein, and out of the localized abscess which formed over it were cultivated perfectly normal, virulent-looking Streptococci. In addition, this child, whose initial septicemia had been cured, developed from that phlebitis a recurrent septicemia which continued in spite of continued drug therapy for many days. She eventually recovered.

It did seem, however, in that case and in a number of other instances, that the presence of an infected thrombus in a large vessel militates very strongly against satisfactory results with sulfanilamide in curing a bacteriemia.

In our own experience, it has been possible for us to believe that, in cases of bacteriemia which have failed to respond to the drug, there was a definite element of suppurative phlebitis. Perhaps it is because the drug does not get at the blood clot and the organisms in the clot or thrombus, or it may be for some other reason.

Doctor Lewis mentioned a very interesting patient with a very prolonged infection. We had, at the Presbyterian Hospital, a patient of Dr. Hugh Auchincloss', who had a very similar infection. In fact, these two children came down with the disease within about a week of each other and their cure was effected at just about the same time. This patient of ours had gone along for six years, during which time she had been in the hospital almost continuously. Her response was equally dramatic, perhaps more rapid because the extent of her disease was not quite so great as it was in Doctor Lewis' case.

Certainly, sulfanilamide has seemed to have no effect on localized Staphylococcic infections. However, reports in the literature and the limited experience of our own hospital have suggested that sulfanilamide may actually have a real place in treating invasive Staphylococcic infections where a high degree of localization with tissue break-down and pus formation have not occurred, factors which even with Streptococcic lesions are thought to interfere with the action of sulfanilamide.

Therefore, I think that in early cases of Staphylococcic osteomyelitis, bacteriemia, and in cases of Staphylococcic cellulitis where there is no localization, treatment with sulfanilamide in the same way as we are using it for Streptococcal infections is indicated and may possibly produce favorable results, whereas, it will fail to work in localized carbuncles and abscesses.

DR. PERRIN H. LONG (closing): Sulfanilamide is so widely used that I cannot resist telling a story that I heard in the Johns Hopkins Hospital exactly a month ago.

A resident from one of the leading Boston hospitals had lunch with me. He said, "You know, the other night at staff meeting, our resident was going over the records and he said, 'Say, do you know what I think? I think we'd better just give everybody who comes to the hospital sulfanilamide and if they're not well in five days, then we'll do a physical examination.'"

I do not think we have gotten quite to that point, but we have come to

the conclusion that if a patient is severely ill and shows the clinical signs of infection which are responding to sulfanilamide, then it is better to treat the patient with sulfanilamide rather than to await the bacteriologic confirmation of the clinical diagnosis. If this is done, valuable time will not be lost and a fatality may be prevented. If, in such an instance, the bacteriologic results do not confirm the clinical impression, then sulfanilamide could be discontinued and no harm will be done.

In the Johns Hopkins Hospital we have had only one patient, who had adequate sulfanilamide therapy, die. I think in our Streptococcal infections this is the only case who should have gotten well and who did not.

We believe that this is probably due to our high dosage and our insistence on high blood levels. We can show in mice, which have no natural resistance to speak of (many of them have none at all), that there is a definite relation between the height of the blood level and recovery from Streptococcal infections. In the clinic, inadequately treated patients, in our experience, do very badly.

Recently, there was a very interesting article that appeared in the Canadian Journal of Medical Research. It has nothing to do with bacteria but it has to do with tomato plants. Doctor Marshall told me about this paper yesterday coming up on the train, in which it was shown that minute amounts of sulfanilamide stimulated the growth of tomato plants. It might turn out that very minute amounts of sulfanilamide might stimulate the growth of bacteria because sulfanilamide in tomato plants behaves very much as a plant hormone does. So I cannot insist too much on our idea of high sulfanilamide blood levels until the infection is under control, and once under control, then we believe that you should discontinue the drug as quickly as possible with safety.

DR. CHAMP LYONS (closing): In answer to Doctor Mellon's question: I do not believe Streptococcal infections in mice are entirely comparable to Streptococcal infections in man, for a number of reasons which cannot be gone into at this time. The discrepancy which he mentioned I believe is due to the fact that Streptococci must be grown continuously for a period of time in the presence of sulfanilamide to maintain this attenuation of virulence, and that in diminishing or low concentrations of the drug, they revert immediately to the virulent phase.

I should like to say, in reply to Doctor Robertson's remark that many of his patients have died, that I believe it likely that they are patients who had no antibody. There are two things, in addition, which I should like to bring up. First of all, patients who receive blood transfusions while they are receiving sulfanilamide therapy should have a determination of their compatibility made with their blood containing sulfanilamide. We have had a few instances in which it looked as if the sulfanilamide in the blood had altered the compatibility of the blood for receiving transfusions.

The second point is that sulfanilamide therapy used for prophylactic purposes requires that the Streptococci must grow in it for a period of time before it can exert its prophylactic effect. A year or so ago, a report was made on the use of sulfanilamide in the treatment of 16 patients with colon bacillus pyelitis. Four of these patients developed an acute hemolytic Streptococcus sore throat during treatment. The subsequent course of the disease was benign and they recovered, but normal Streptococci were able to implant themselves on a body tissue already saturated with sulfanilamide. After growing in the presence of the drug, they were altered and killed.

TREATMENT OF HEMATOGENOUS NEPHRITIS WITH SULFANILAMIDE*

CASE REPORT

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THE FOLLOWING case, and the accompanying chart which contains exhaustive clinical details, emphasize the value of sulfanilamide in complicated renal infections following postoperative septicemia, and demonstrate the importance of chemical and bacteriologic studies in order to direct the treatment intelligently.

Case Report.—B.U.I. No. 26884: W. E. M., male, age 59, entered the Brady Urological Institute April 26, 1938, complaining of difficulty and frequency of urination, and, recently, complete retention. His general condition was excellent. Examination of the chest and abdomen was negative. Blood pressure 130/95; pulse 88. The peripheral vessels were moderately sclerotic. The genitalia were negative. Rectal examination revealed a considerably enlarged, smooth, elastic prostate with areas of induration in the lateral lobes and also in the seminal vesicles. Prostatic secretion, obtained by massage, contained pus cells. *Diagnosis:* Benign prostatic hypertrophy and prostatitis. A posterior cysto-urethroscope entered easily and recovered 20 cc. residual urine. The capacity of the bladder was 300 cc. Rounded median and lateral lobes were present and partially obscured the trigone which was moderately hypertrophied. The ureteral orifices appeared normal.

The patient left the hospital for four weeks and returned May 27, 1938, for operation. At the time of readmission, the retention of urine was complete and, on catheterization, 1,050 cc. were recovered. On the following day, catheterization was again necessary, 900 cc. urine being removed. Cultures of the urine were reported sterile, but on May 28, 1938, the temperature rose to 101.4° F. The phthalein test showed an appearance time of six minutes, and half-hour excretions of 50, 12, 8 and 5 per cent, making a total of 78 per cent in two hours. Blood urea 28 mg.; hemoglobin 90 per cent; white blood cells 7,600. The urine was clear, acid, specific gravity 1.010, no albumin or sugar; no white or red blood cells or bacteria were found on microscopic examination. On May 29, 1938, the temperature did not go over 100° F., and on the following day the patient was afebrile. Culture of the urine was again reported sterile.

Operation.—May 31, 1938: Dr. Hugh H. Young. Under spinal anesthesia, the prostate was exposed through a curved perineal incision. An incision through the apex of the prostate on the right side was made for introduction of the tractor, and the lateral and median lobes were easily enucleated through bilateral capsular incisions. The hemorrhage was slight, but the Davis bag and tube were inserted for hemostasis and drainage. After approximating the levator ani muscles with plain catgut, the skin was closed with interrupted sutures of silk, and drainage was provided through the right-angle of the wound. There was no appreciable change in the blood pressure or pulse during the operation. Microscopic examination of the tissue removed showed benign prostatic hypertrophy and chronic prostatitis.

Subsequent Course.—The patient was returned to the ward in good condition, but by midnight the temperature had risen to 101.4° F. Numerous clinical and laboratory

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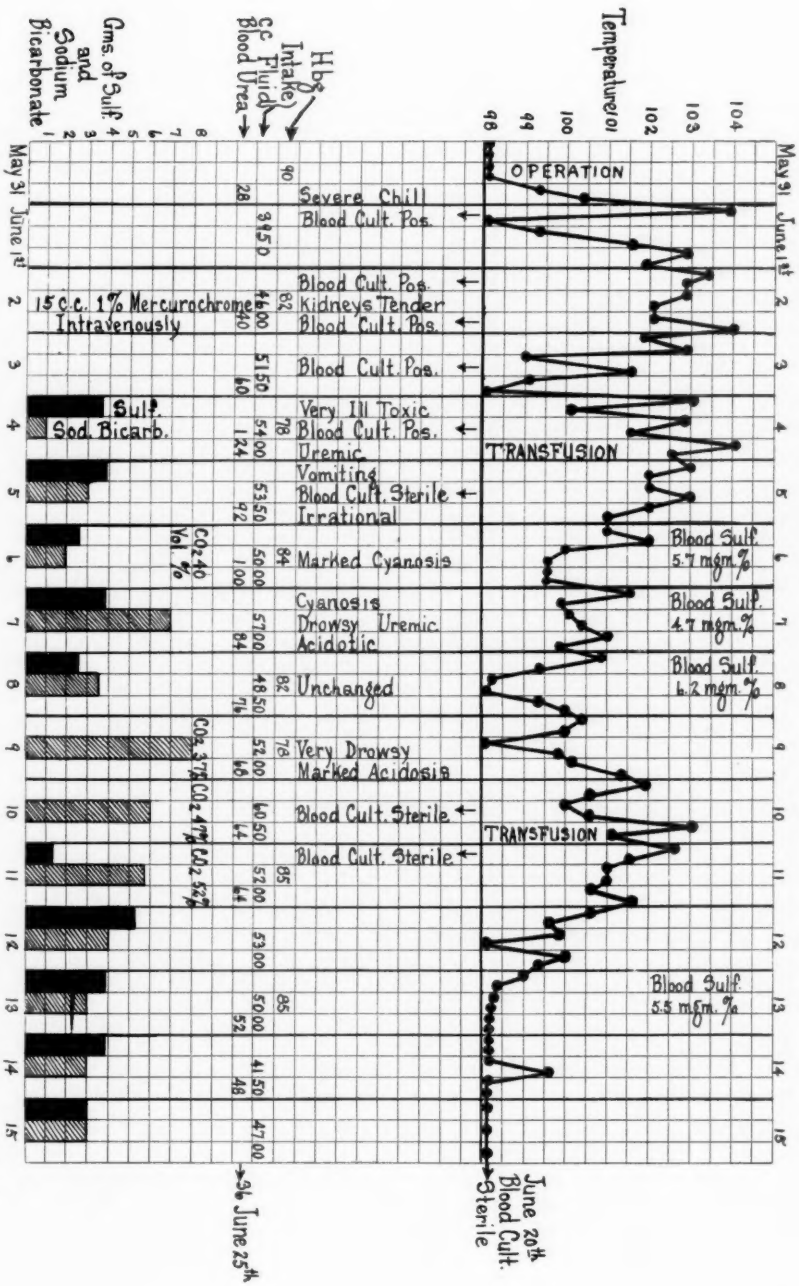

CHART 1.—Showing graphically the variations in the temperature, condition of patient, laboratory data, therapy employed and results.

data, together with the temperature curve, are detailed in Chart 1, on which is recorded the condition of the patient from day to day, the hemoglobin, amount of fluid taken by mouth, subcutaneously or intravenously, the dosage of sulfanilamide and sodium bicarbonate, the blood sulfanilamide in milligrams per cent, the carbon dioxide combining power, and the blood transfusions. Many of these data, therefore, have been omitted from the daily comments on the patient's progress. The chart graphically shows the onset of septicemia and suppurative nephritis; sterilization of the blood by chemotherapy, but persistence of the nephritis, culminating in uremia; the excellent effect of sulfanilamide, until the patient developed acidosis and a marked drop in hemoglobin, which required blood transfusions.

June 1: The patient had a chill and rise of temperature to 103.8° F. at 4 A.M. A blood culture was taken and subsequently showed a massive growth of *B. Aerobacter aerogenes* (*B. lactis aerogenes*). The temperature dropped to normal, but by 8 P.M. it had reached 102.8° F. The Davis hemostatic bag and tube were then removed.

June 2: At 8 A.M. the temperature was 102.8° F. Blood cultures taken at this time again showed *B. Aerobacter*. The abdomen was distended and both kidneys were markedly tender. The blood urea had risen to 40 mg. In order to combat the septicemia the patient was given an intravenous injection of 15 cc. of 1 per cent mercurochrome at 11 A.M. There was the usual "postinjection" rise of temperature, which reached 104° F. at 8 P.M., followed by a rapid drop, which reached 99° F. at 8 A.M. the following day. Cultures taken on June 2 and 3 were still positive, but the number of colonies had greatly diminished.

June 4: The patient appeared desperately ill. He was toxic, drowsy, hiccoughing and perspiring profusely. The temperature was 104.2° F. There was little secretion of urine and the blood urea was 124 mg. Blood cultures taken at 10 A.M. were reported positive. At 9 P.M. the patient was given sulfanilamide (Prontylin) 3.6 Gm. by mouth, and sodium bicarbonate, 1 Gm. His condition was so desperate that a transfusion of 600 cc. of citrated blood was given, as shown in the chart, which records all the laboratory reports.

June 5: The patient continued toxic, drowsy, nauseated and unresponsive. The temperature was 103° F. The blood urea was still elevated (92 mg.). A blood culture taken at 9:30 A.M. was reported sterile. At 11 A.M. the patient was given sulfanilamide, Gm. 1.3, and sodium bicarbonate, Gm. 1, in water (150 cc.). This dosage was repeated at 4:30 and 10 P.M.

June 6: The patient was somewhat better; there was more urinary drainage and less tenderness over the kidneys. Blood urea 100 mg.; hemoglobin 84 per cent. The free blood sulfanilamide was 5.7 mg. per cent. The patient was markedly cyanotic. The CO_2 combining power at 9:30 A.M. was 40 volumes per cent. The patient was given sulfanilamide, Gm. 2.6, and sodium bicarbonate, Gm. 2.

June 7: The patient remained very drowsy and showed clinical evidence of acidosis. The free blood sulfanilamide was 4.7 mg. per cent. The blood urea was 84 mg. The temperature varied from 98.8° to 101.6° F. Although the blood cultures had been reported sterile, it was apparent from the continued high blood urea and marked evidence of uremia that a renal infection (pyelonephritis) was present and that continuation of sulfanilamide therapy was imperative. The patient was given sulfanilamide, Gm. 3.8, and, on account of the acidosis, sodium bicarbonate, Gm. 7, in divided doses. The free blood sulfanilamide was 4.7 mg. per cent. The urinary output increased to a good volume.

June 8: The temperature ranged from normal to 100.8° F. The blood urea dropped slightly to 76 mg. The blood sulfanilamide was 6.2 mg. per cent, but the patient was very cyanotic, obviously in marked acidosis, restless with deep respirations; nevertheless, on account of the evident suppurative nephritis, sulfanilamide was continued, Gm. 2.6, and sodium bicarbonate, Gm. 3.6.

June 9: The patient continued restless and drowsy, acidotic, but took fluids well.

The blood urea was 68 mg. The CO_2 combining power had dropped to 37 volumes per cent. On this account the sulfanilamide was discontinued. The patient was given sodium bicarbonate, Gm. 8, in divided doses.

June 10: The patient showed marked anemia (Hb. 64) and was given 600 cc. citrated blood, and sodium bicarbonate, Gm. 6. No sulfanilamide was given. The temperature rose to 103° F., but the blood culture remained sterile.

June 11: The patient was improved. The hemoglobin was 85 per cent and the blood urea 64 mg. There was no evidence of acidosis, but the temperature rose to 102.6° F., and it was apparent that additional sulfanilamide was indicated to combat the renal infection. The patient was given sulfanilamide, Gm. 1.3, and on the following day the blood sulfanilamide was 5.3 mg. per cent. This was accompanied by a drop in temperature, the highest being 100.6° F. After this the patient was given intensive treatment with sulfanilamide and the temperature rapidly approached normal, as shown in the chart.

June 12: The patient was given sulfanilamide, Gm. 3.8, and sodium bicarbonate, Gm. 4.

June 13: Sulfanilamide, Gm. 3.8, and sodium bicarbonate, Gm. 3, were given. The blood sulfanilamide was 5.5 mg. per cent. The blood urea was 52 mg.

June 14: The temperature was normal and the patient felt fine. The tenderness over the kidneys had disappeared. The blood urea was 48 mg. The patient was given sulfanilamide, Gm. 3.8, and sodium bicarbonate, Gm. 3.

June 15: The temperature, pulse and respirations were normal. The patient sat up in bed, and his appetite was excellent, but regardless of his general condition it was considered unsafe to discontinue the sulfanilamide. He was given sulfanilamide, Gm. 3, and sodium bicarbonate, Gm. 3.

June 16: Inasmuch as the patient continued to improve, sulfanilamide was discontinued. By June 21, the blood urea had become normal; blood pressure 130/70; hemoglobin 85 per cent. The patient's general condition was excellent and he voided 2,950 cc. of urine in 24 hours.

June 27 to July 8: The patient continued to improve. The perineal wound, treated frequently with 2 per cent mercurochrome, had healed and he voided about 4,000 cc. of urine daily. Blood urea 36 mg.; hemoglobin 85 per cent. The phthalein test showed excellent renal function, which was the same total as on admission, but cultures of the urine still showed the presence of *B. Aerobacter aerogenes* and a few white blood cells. The patient left the hospital on July 8, 1938. The operative result was excellent and he was voiding normally. On September 25 he was reported to be well.

Discussion.—Clinically, the patient appeared to have completely recovered from his renal infection, but it was not determined whether the infection was entirely vesical or also involved the kidney. It is evident that a massive blood stream infection developed shortly after operation, as a result either of bacteria involved in the chronic prostatitis, or the catheterization before operation which was followed by fever. Not infrequently, after urethral instrumentation, cystoscopy or even simple catheterization, a so-called "urethral chill," followed by high temperature and positive blood cultures, occurs. As a rule, the blood stream infection is transitory, but in our case it is apparent that a pyelonephritis developed rapidly, and presented the most serious problem during the postoperative course. The rapid increase in blood urea, the development of acidosis and the steady drop in hemoglobin presented very serious problems which required the most painstaking laboratory studies to determine just what form of therapy was indicated from day to day. The use of sulfanilamide was followed by a rapid sterilization of the blood, but the infection of the kidneys persisted, as

shown by the continuation of the temperature, the progressive increase in the blood urea, the development of pronounced uremia and drop in hemoglobin. To combat this, the continuation of an adequate dosage of sulfanilamide was necessary, but this precipitated an acidosis which finally made it necessary to discontinue the sulfanilamide and greatly increase the ingestion of sodium bicarbonate. When the acidosis was reduced, the continuation of the fever and high blood urea made it imperative to resume the sulfanilamide therapy which, fortunately, was followed by a progressive drop of the temperature to normal and was not accompanied by acidosis. While undergoing intensive treatment with sulfanilamide, the patient went on to rapid recovery, with a return of the blood urea and hemoglobin to normal. Without the assistance of the laboratory to determine the blood sulfanilamide content and the CO_2 combining power, as well as the various methods of estimating renal function, this case could, probably, not have been brought to a successful termination.

We are indebted to the Winthrop Chemical Company for the sulfanilamide (Prontylin) used in this case, and for a grant for research.

THE TREATMENT OF INTRAPERITONEAL ABSCESS ARISING FROM APPENDICITIS

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EARLY in 1936, an abrupt change occurred at the University of Virginia Hospital in the method of treatment of abscess resulting from appendicitis. Although for several years the practice had been followed of allowing poorly localized intraperitoneal infections to become definite abscesses before operating, the conservative treatment of cases of appendicitis presenting a mass began at this time to be prolonged. It was apparent that many of these cases, as shown by others, could be discharged from the hospital practically well without the necessity of operating. These cases were instructed to return for interval removal of the appendix just as is the common practice when abscesses have been drained surgically. After two years of the practice it was thought wise to determine by an appraisal of the actual results whether in our hands expectant treatment of an appendiceal mass had justified itself. The results of the appraisal seem to confirm the clinical impression that this method is the method of choice.

MATERIAL.—The material on which this analysis is based consists of all cases of acute appendicitis admitted to the hospital during the five year period 1933–1937, a total of 1,069 cases. Only those cases are included which, after appendicectomy, were reported by the pathologist as showing microscopic changes of acute disease, or that without operation presented a clinical picture to be defined. This resulted in the exclusion of all cases of frank or doubtful chronic appendicitis. In 240 of the 1,069 cases, infection had spread beyond the appendix as described below. One hundred and eighty-one cases of the 240 were diagnosed as intraperitoneal abscess.

Classification.—In agreement with Schullinger's[1] implications, it is felt that lack of clarity and uniformity of definition of the pathologic stages of appendicitis is partly responsible for widely differing opinions on treatment following perforation. For this reason a careful attempt has been made to define the grades of appendicitis as classified in the present study. Whenever possible, an individual case has been placed in the less advanced group. For instance, many cases of perforation, which recovered promptly following early operation, are classified as simple acute appendicits, inasmuch as they presented no evidence of an established peritonitis.[2, 3] Although more careful study has been given to the hospital records of the 240 cases with extra-appendiceal peritoneal infection, the operator's note, the pathologist's report and the temperature chart have been reviewed in the remaining 829 histories.

The cases have been grouped in three classifications (Table I):

Group I.—Simple Acute Appendicitis: In the cases in this group operation was performed immediately on admission to the hospital. They include: (a) Cases which presented on microscopic examination acute or subacute appendicitis without perforation; (b) cases presenting perforation or gangrene of the appendix, in which the postoperative course demonstrated no independent peritoneal infection; and (c) cases presenting perforation at operation, in which the appendix was completely separated from the general peritoneal cavity by being enveloped in the omentum.

Group II.—Appendicitis With Abscess: This group includes: (a) Cases that presented an abscess at operation; and (b) unoperated cases, which on admission presented a characteristic clinical picture, *i.e.*, a typical history, definite sepsis, localized tenderness and the outline of a mass in the right lower quadrant.

Although it may well be pointed out that the diagnosis of appendicitis was not proven in these latter cases, yet the fact that the masses disappeared under conservative treatment with accompanying disappearance of the signs of sepsis argues strongly against their having been confused with other less common causes of right lower quadrant tumefaction. Assuming that all the masses on which diagnoses were based were the result of appendicitis, a doubt remains as to their all being true abscesses. Many may well have represented a diffuse inflammatory reaction agglutinating loops of bowel or a mass of omentum surrounding the diseased appendix. Some observers[4, 5] assume with no definite proof that any mass which disappears gradually without operation is *ipso facto* not an abscess. Others[6, 7] take the point of view, which seems more reasonable to us, that the line between abscess and nonabscess cannot be clearly drawn from clinical criteria. Whereas, doubt as to the presence of pus is unavoidable, it will be seen as the argument proceeds that the question is practically unimportant, since the choice of treatment must depend on the clinical findings, and the results of treatment are of significance only as they refer to the clinical findings. With the implied reservation that true abscess may not always be present, the term will be used to designate the clinical class as defined above.

Group III.—Appendicitis With Diffuse Peritonitis: This group includes cases presenting clinical evidence of peritonitis extending beyond the right lower quadrant.

No attempt has been made to define the extent more accurately, inasmuch as on clinical and operative findings sharper definition is often impossible. In this group is found a small proportion in which appendicitis has not been definitely proven as the cause of peritonitis. Three or four cases of clinical general peritonitis have been excluded because of atypical history or of some other possible source of peritonitis. In many of the cases included in this group, localization of the infection to single abscesses occurred; these cases thereafter presented a problem similar to those of Group II.

METHODS OF TREATMENT.—Five programs of treatment have been recognized in the cases of extra-appendiceal involvement (Table I).

Immediate Operation: Forced.—Cases are included under this heading in which immediate operation was decided upon, not because of the stage of the abscess or the accepted current practice, but because of unmistakable indications for surgical intervention.

In the abscess group, two cases presented with acute intestinal obstruction and one with a subcutaneous communicating abscess close to rupture. These three cases obviously have no bearing on the problem of conservative versus operative treatment of abscess and will be no further considered except as they affect the mortality of the series.

Immediate Operation: Elective.—Operations in this group were performed on admission, particularly in the earlier years, on the basis of what we then considered established surgical principles. In the abscess group, they represent cases presenting well localized masses of some days' standing.

A few cases, especially those of the later years, represent instances of failure to diagnose abscess preoperatively. The term "immediate," as applied in the abscess group, does not imply an emergency procedure; but all operations were done within 24 hours of admission to the hospital.

TABLE I

INCIDENCE OF CHOICE OF THERAPEUTIC PROCEDURE BY YEARS

	Group I	Group II Abscess					Group III Diffuse Peritonitis				
	Simple Acute Appendicitis	Immediate Operation		Conservative Treatment Begun			Immediate Operation		Conservative Treatment Begun		
				Operation					Operation		
Year	Immediate Operation	Forced	Elective	Elective	Forced	No Operation	Forced	Elective	Elective	Forced	No. Operation
1933	202	2	39	3	2	0	0	9	4	2	1
1934	128	0	25	7	1	3	0	6	1	3	1
1935	164	0	23	3	3	3	0	4	1	3	0
1936	148	0	8	1	6	22	0	4	0	5	3
1937	187	1	3	1	5	20	0	7	0	4	1
Totals	829	3	98	15	17	48	0	30	6	17	6

Conservative Treatment Begun; Operation: Elective.—In this group are included the cases presenting marked sepsis and evidence of incomplete localization of abscess, which, after a few days of conservative treatment, showed diminished sepsis and a sharply localized mass, and which were then operated upon as a matter of principle. It was believed at the time of treatment that these cases had shown maximum improvement and that, therefore, the optimum time for operation had arrived.

Conservative Treatment Begun; Operation: Forced.—This group includes cases presenting on admission evidence of either a well localized or a poorly localized abscess. Under conservative treatment the course of the disease took an unfavorable direction, and operation seemed indicated on unquestioned surgical principles.

These indications included acute intestinal obstruction, growth in size of the abscess, and threatened perforation of the abscess into the abdominal wall or the rectum, usually accompanied by increasing signs of sepsis. The written opinion of the operator was not taken alone as proof positive of the enforced nature of the operation, but his opinion was combined with the recorded changes in the patient's general and local condition.

Conservative Treatment Begun; No Operation.—The cases in this group fulfilled the requirements for the diagnosis of abscess or diffuse peritonitis, and in none was operation performed before discharge.

General Considerations of Treatment.—Expectant treatment followed the Ochsner[8] principles, modified by modern resources in maintaining physiologic balances: Nothing is allowed by mouth until the highest daily temperature comes to within about one and one-half degrees (Fahrenheit) of normal, the mass has definitely shrunk, and tenderness is slight or absent, when sips of water are permitted. Each day during the period of starvation at least 3,500 cc. of water, containing about 100 Gm. of glucose and 13 Gm. of salt, are given intravenously to the average adult. If edema occurs, about 75 Gm. of glucose are substituted for the salt. The serum protein and blood chlorides are watched after the first week, and the daily urine volume throughout. The actual intake of water and crystalloids is governed by these observations. Transfusions are given freely as indicated by anemia, hypoproteinemia or continued sepsis. Morphine is employed until favorable progress is definite. In the established abscess we see no value in Fowler's position. After water is started by mouth, other liquids may follow in a few hours and later a soft hospital diet, unless unfavorable symptoms intervene. Enemata are used as sparingly as possible and duodenal suction is employed for distention and vomiting. The patients are watched very closely for the signs that suggest an impending enforced operation. In general, the patient is discharged when the temperature goes no higher than 99.0° F., and the mass has lost all its tenderness and can be felt with difficulty or not at all. At this time the leukocyte count has usually approached, or reached, the normal level. As experience increases with the method of prolonged conservative treatment, the indications for forced operation are becoming more strict. Whereas, earlier a rise of temperature for a day or so might be interpreted as indicating a necessity for operation, now, moderate pyrexia must be accompanied by objective signs of spreading infection.[7]

Except for choice of incision, technical operative procedures have been uniform. Practically all operations have been performed under spinal anesthesia, except in small children. Two types of incision are used, the McBurney, and a short right midrectus with retraction of the muscle toward the right. The appendix is removed whenever a search is not contraindicated by the patient's general condition or, in a few instances, when it is judged the local peritoneal reaction should not be greatly disturbed. With the exception of not more than ten or 12 instances in this series, the peritoneal cavity has been drained only when actual granulation tissue is present. In perforated or gangrenous appendicitis the wound is frequently drained to the level of the peritoneum.

Postoperative care has also been uniform. All cases with peritoneal contamination, including the borderline cases placed in Group I, are treated for a few days by the methods used in nonoperative treatment.

Change in Method.—The change in the preferential method of treating

abscess, from immediate operation in well localized cases or elective, delayed operation in those poorly localized, to nonoperative treatment in all cases if possible, forms the chief basis of comparison in the present study (Table I). It is seen that, during the years 1933–1935, only 22.3 per cent of abscess cases were treated by conservative measures at the outset, and only 6 per cent were carried through without operation. Most of the former were cases poorly localized on admission, and of the latter, cases in which the abscess disappeared suddenly by rupture into the bowel, cases that refused operation and cases in which contraindications to operation existed. By contrast, in the years 1936–1937, in 83.3 per cent of abscesses, conservative treatment was started, and 65 per cent were carried through without operation. A few cases are seen to have been treated by elective operation during these latter years; the majority of these were in the somewhat transitional year of 1936.

The distribution of choice of methods of treatment in the diffuse peritonitis group (Table I) indicates no corresponding change in policy. Throughout the five year period the preferential immediate treatment of diffuse peritonitis has been nonoperative, and deviations from this course have resulted from diagnostic difficulties and the varying nature of the material.

Methods of Statistical Analysis.—*Statistical Validation.*—No unqualified conclusion, based on a comparison, is expressed unless the actual difference is more than twice the standard error of the difference, a ratio which is generally accepted as indicating a high probability of significance. Those data in which statistical validation has not been attempted or in which its results show that no significance attaches to the differences presented, will be indicated in the text. For purposes of clarity, the various standard errors have been omitted from the tables.

Mortality.—The data presented bear largely on the appraisal of the results of nonoperative treatment in abscess. There is presented in addition a survey of the percentage incidence of admission of cases of all three groups year by year and of the corresponding mortality rates, for the purpose of furnishing a background for the special group to be considered, and of indicating the grade of success which the service attains in the treatment of appendicitis as a whole.

Morbidity.—The measures of morbidity employed in estimating the results of treatment are: (1) Days of hospital stay; (2) days of fever; (3) days of duration of drainage; and (4) number of complications and sequelae. The first three of these have been calculated only on the surviving cases. The complications have been computed in both living and dead cases.

(1) Hospital Days: These include the day of admission and the day of discharge.

In the few cases which were transferred from other services to the department of surgery, the hospital days were numbered from the date of consultation to the date of discharge from the hospital.

(2) Days of Fever: Absence of fever has been strictly interpreted as representing the first day during which the mouth temperature did not

exceed 98.6° F. at any of the four daily readings. If after a day or two of normal temperature, fever again appeared, these days were included as days of fever. Inasmuch as many patients during the last hospital day presented mouth temperature readings slightly over 98.6° F., the exact duration of fever is often unknown. This has been indicated by computing the percentage of patients in each group whose temperatures had not come down to a conventional, strictly normal level before discharge.

(3) Days of Drainage: The exact termination of drainage in the hospital is difficult to determine from the records, because of differing definitions of the term. There is opportunity for error in the averages computed, but the opportunity is equally distributed in each group studied and the errors should tend to cancel each other. The problem of lack of knowledge of the termination of drainage, when cases were discharged to the family physician for home care, has also been met by computing the percentage of cases draining on discharge and not reporting to the hospital outpatient department.

(4) Complications and Sequelae (Table VI): The recorded complications and sequelae, compiled from hospital notes and postmortem reports, have been divided into three categories: (1) Complications and sequelae directly related to appendicitis through the spread of infection to the peritoneum, the portal system or the wound, including abscess in the wound, the cecal gutter, the pelvis, the liver or the subphrenic area, intestinal obstruction during the acute phase of the disease or months later, paralytic ileus, fecal fistula and postoperative ventral hernia; (2) complications indirectly related to the disease, including pneumonia, pulmonary collapse, pleurisy, empyema, thrombophlebitis and suppurative parotitis; and (3) complications unrelated to appendicitis, such as diabetes, pregnancy, syphilis, fibromyoma uteri, etc. The combined number of complications under the first two headings was calculated per patient in each group studied.

Miscellaneous.—In addition to the comparisons of mortality rates and morbidity factors, two closely related problems have been investigated: (1) The success of nonoperative treatment in the extreme age-groups as compared to that in the middle age-group; and (2) the apparent effect on the later history of the patient of the failure to remove the appendix, both when an abscess was drained and when no operation was performed.

TABLE II

INCIDENCE OF TYPES OF APPENDICITIS ENCOUNTERED BY YEARS

	Appendicitis; Peritoneal Infection				
Year	Simple Acute	Abscess	Diffuse Peritonitis	Total	Total
1933	202—76.5%	46—17.4%	16—6.1%	62—23.5%	264
1934	128—73.1%	36—20.6%	11—6.3%	47—26.9%	175
1935	164—80.4%	32—15.7%	8—3.9%	40—19.6%	204
1936	148—75.1%	37—18.8%	12—6.1%	49—24.8%	197
1937	187—81.7%	30—13.1%	12—5.2%	42—18.3%	229
Totals	829—77.5%	181—17.0%	59—5.5%	240—22.5%	1,069

RESULTS.—*Mortality in General.*—The distribution of diagnoses between simple and complicated appendicitis shows fluctuations from year to year (Table II). In interpreting these figures, the stringent requirements for cases to be included in Groups II and III, as already defined, must be remembered. The apparently not unusual average incidence of appendicitis with extra-appendiceal infection (22.5 per cent) in this series must be interpreted as relatively high. Although not statistically determined, it is believed that the inclusion of all perforated cases in these groups, under the definitions presented by many other authors, could easily raise this percentage to nearly 40 per cent of the total cases. It is interesting that Stone,[9] using the conventional division of appendiceal from extra-appendiceal infection, reported from this clinic, in 1935, an incidence of 38 per cent of perforated appendices.

TABLE III

MORTALITY BY TYPES OF APPENDICITIS AND BY YEARS

Year	Simple Acute			Appendicitis: Peritoneal Infection									Total		
				Abscess			Diffuse Peritonitis			Total					
	Cases	Deaths	Mortality Percentage	Cases	Deaths	Mortality Percentage	Cases	Deaths	Mortality Percentage	Cases	Deaths	Mortality Percentage	Cases	Deaths	Mortality Percentage
1933	202	0	0	46	1	2.2	16	7	43.8	62	8	12.9	264	8	3.0
1934	128	2	1.5	36	3	8.3	11	6	54.5	47	9	19.1	175	11	6.3
1935	164	0	0	32	1	3.1	8	2	25.0	40	3	7.5	204	3	1.4
1936	148	0	0	37	2	5.4	12	6	50.0	49	8	16.6	197	8	4.0
1937	187	0	0	30	2	6.6	12	3	25.0	42	5	11.9	229	5	2.2
Totals	829	2	0.24	181	9	5.0	59	24	40.6	240	33	13.7	1,069	35	3.27

The mortality rate for the entire group of 1,069 cases is 3.27 per cent (Table III), a figure that compares favorably with average statistics. Two deaths occurred in the simple acute group (0.24 per cent), representing the hazards of any operative procedure. One case died of a rapidly progressive pneumonia following pulmonary collapse on the fourth postoperative day, and the other of an overwhelming Streptococcus infection of the abdominal wall. The mortality in the abscess group (5 per cent) is not far above the general average for this series. In the diffuse peritonitis group, however, a high death rate (40.6 per cent) is to be noted. This is, in large part, explained by the method of classification.

Rather marked fluctuations (from 1.4 to 6.3 per cent) are seen in the yearly mortality. These figures and the data on the yearly incidence of complicated appendicitis can be shown to have a high coefficient of correlation. Direct variation of an almost linear character apparently occurs (Chart 1). An increase in the relative number of complicated cases is associated with a corresponding increase in the mortality rate for the year, and vice versa, independent of any change in methods of treatment. The present analysis of this relationship only confirms an often previously noted correlation.

Treatment of Abscess.—The assembled data in the abscess group of 181 cases reveal interesting differences in mortality and morbidity following different therapeutic programs (Table IV). (No statistical computations have been made involving the first column, as indicated earlier.) The differ-

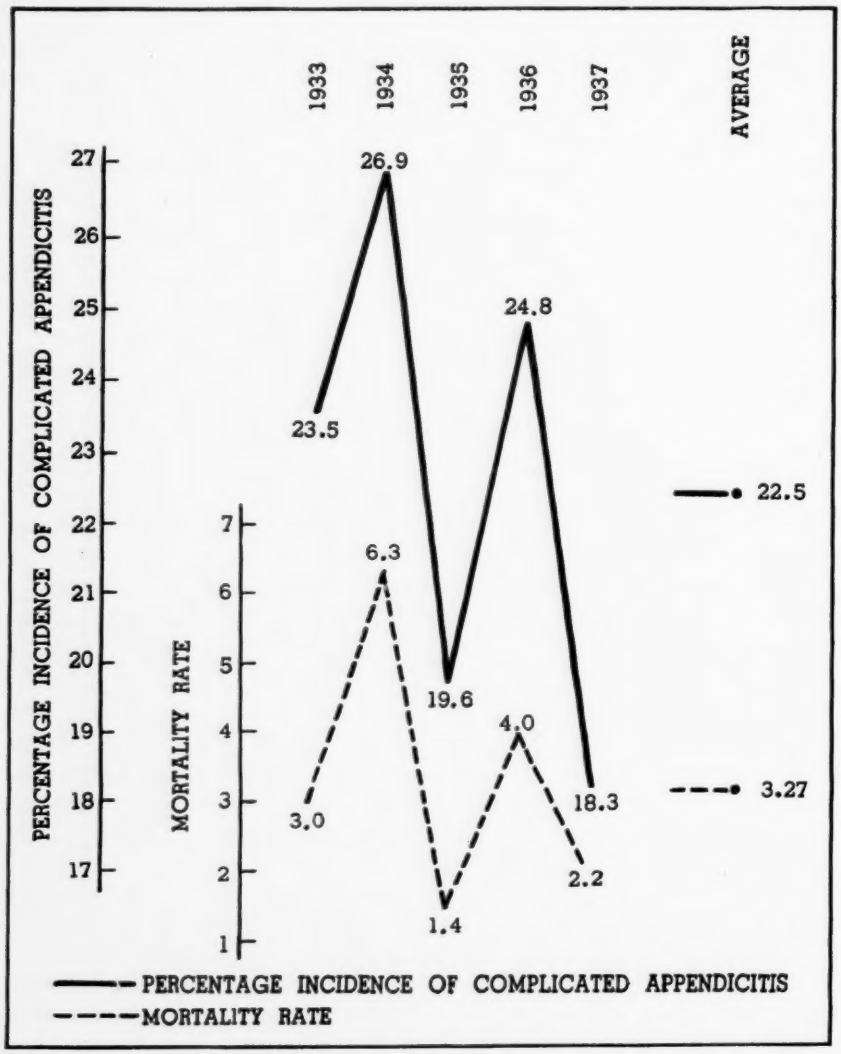

CHART 1.—Correlation of yearly admission rate of complicated appendicitis, *i.e.*, with diffuse peritonitis and abscess; and the total yearly mortality from appendicitis.

ences between all the mortality rates presented are statistically significant except for the comparison between the mortality rate of the group that underwent forced operation after initiation of conservative treatment and the mortality rates of the other groups. In other words, it can be stated with some positiveness, that the absence of mortality in the cases treated without

TABLE IV

GROUP II: ABSCESS

MORTALITY AND MORBIDITY FOLLOWING VARIOUS THERAPEUTIC PROCEDURES

	Immediate Operation		Conservative Treatment Begun		
			Operation		No Operation
	Forced	Elective	Elective	Forced	
	Data on Total Cases				
Number of cases	3	98	15	17	48
Complications per patient	1.66	.63	.60	.94	0
Deaths	1	4	3	1	0
Mortality	33.3%	4.0%	20.0%	5.9%	0.0%
	Data on Living Cases				
Number of cases	2	94	12	16	48
Average days in hospital	32	19.5	30.6	27.8	11.9
Average days of fever	29	17.7	25.2	25.8	9
Per cent of cases discharged with fever	0.0	46.9	16.6	56.0	31.2
Average days of drainage known	28.5	20.1	22.2	41.3	0
Per cent of cases in which date of termination of drainage is unknown	50.0	76.5	58.3	75.0	0.0

operation as compared with the mortality of 4 per cent in those treated by immediate elective operation and of 20 per cent in the small number treated by late elective operation, represents a significant difference in results associated with the differences in treatment. All of the morbidity factors, including complications (but excluding the percentages of unknown duration of fever and drainage) present statistically significant differences, with the exception of the unimportant comparison between late forced and late elective operation where the actual differences are small. One may state, therefore, that the absence of complications, the short hospital stay, the brief period of pyrexia and the absence of any period of drainage in the cases treated without operation represent real differences over the corresponding figures for forced late operation, and for either of the elective groups. For instance, the non-operative group shows no complications as against 0.63 complications per patient in the cases electively operated upon on admission, 11.9 days in the hospital as against 19.5 days, nine days of fever with 31.2 per cent unknown durations as against 17.7 days with 46.9 per cent unknown durations, and no days of drainage as against 20.1 days with 76.5 per cent unknown durations. It is perfectly unmistakable from this and further comparisons to be made in Table IV that *successful* conservative treatment is the most desirable method of treating this group of cases not only from the point of view of the prospect for recovery but also from the point of view of the severity of the patient's illness and the cost of hospitalization, to add nothing of the pain, odor, nuisance and expense associated with a drained abscess.

But, of course, this striking comparison does not present the whole story. If a group of cases is started on conservative treatment, a proportion will not do well and will require operation. In this series, of those so started, 60 per cent were successfully carried through, 18.8 per cent had elective operations after success was probable, and 21 per cent came to forced operation (Table VII). In view of the early behavior of cases in which operation was elected after marked improvement, it is probably fair to say that not more than a total of 25 per cent of conservative starts would be unsuccessful. A complete estimation of the results of conservative treatment must compare the combined results of successful and unsuccessful conservative treatment with those of all elective operations. Only in this way can one judge the propriety of initiating conservative treatment as the preferred program for appendicitis with abscess.

TABLE V

GROUP II: ABSCESS

RESULTS FOLLOWING THE INITIATION OF CONSERVATIVE TREATMENT WITH SUCCESSFUL AND UNSUCCESSFUL GROUPS COMBINED, AS COMPARED TO RESULTS FOLLOWING ALL ELECTIVE OPERATIONS

	Conservative Treatment: No Operation and Operation Forced (Combined Columns 4 and 5, Table IV)	Elective Operation: Immediate and Late (Combined Columns 2 and 3, Table IV)
Data on Total Cases		
Number of cases	65	113
Complications per patient	.25	.63
Deaths	1	7
Mortality	1.5%	6.2%
Data on Living Cases		
Number of cases	64	106
Average days in hospital	15.8	20.7
Average days of fever	13.2	15.9
Per cent of cases discharged with fever	37.5	45.3
Average days of drainage known	10.3	20.3
Per cent of cases in which date of termination of drainage is unknown	18.7	83.9

Such a comparison (Table V) reveals that the elective group suffers over twice as many complications as the combined nonoperative and forced delayed operative groups, remains in the hospital about one-third more days, is febrile almost 25 per cent longer, and drains practically twice as long. These figures in themselves, being all statistically significant comparisons, are striking evidence of the value of conservative treatment. The fact that the mortality is over four times as great in the elective operation group as in the conservative group must not be accepted too confidently, since the ratio of the difference to the standard error is just below two. However, the probability that the difference is not due to chance is high, and the figures, taken with the statis-

tically validated comparisons from the same table, are extremely suggestive. It may fairly be said that the results of the conservative regimen do not result in a higher mortality than the results shown by the electively operated cases, that probably the mortality is lower, and that the morbidity is strikingly less in all the measured factors. Inasmuch as the nonoperative cases leave the hospital in the possession of a diseased appendix, the possible later mortality and morbidity in this group must be considered a part of the problem and will so be considered below.

TABLE VI

TABULATION OF COMPLICATIONS AND SEQUELAE DIVIDED ACCORDING TO METHODS OF TREATMENT

	Group II: Abscess				
	Immediate Operation		Conservative Treatment Begun		
			Operation		No Operation
Nature of Complication or Sequela	Forced	Elective	Elective	Forced	
Total Cases	3	98	15	17	48
Complications and Sequelae Directly Related to Appendicitis					
Residual abscess*	2	23	5	9	0
Subphrenic abscess	0	3	0	2	0
Gas gangrene	0	0	0	1	0
Obstruction in acute phase	1	2	0	0	0
Obstruction later	0	2	0	0	0
Paralytic ileus	0	13	1	1	0
Fecal fistula	0	6	1	1	0
Hernia, postoperative	0	3	0	0	0
Totals	3	52	7	14	0
Complications Indirectly Related to Appendicitis					
Pneumonia	1	3	1	0	0
Pulmonary collapse	0	0	0	1	0
Pleurisy; empyema	1	1	0	1	0
Thrombophlebitis	0	4	1	0	0
Parotitis	0	2	0	0	0
Total; both groups	5	62	9	16	0
Average complications per patient	1.66	.63	.60	.94	0
Complications Unrelated to Appendicitis					
	1	9	2	2	6

* Includes abscess in wound, right lower quadrant, cecal gutter, pelvis, liver, *etc.*

Nonoperative Treatment of Abscess in Relation to Age of Patient.—It is, of course, a repeated surgical observation that patients at the extremes of life who suffer from appendicitis are sicker than those in the middle age-group. In this hospital, for instance, the mortality reported, in 1935, by Stone[9] was for children 7.7 per cent as against 2.9 per cent for adults and

3.4 per cent for the entire material. Assuming the superiority of conservative treatment over operative treatment as a generally preferred program, it becomes important to determine whether age should influence the decision against an attempt at nonoperative handling.

TABLE VII

COMPARISON OF SUCCESS OF CONSERVATIVE TREATMENT OF ABSCESS IN DIFFERENT AGE-GROUPS

		Conservative Treatment Begun			
Age-Groups	Total	No Operation	Operation Forced	Operation Elective	Deaths
1–12 yrs.	7	3—42.9%	3—42.9%	1—14.2%	0
13–54 yrs.	57	38—66.7%	10—17.5%	9—15.7%	3
55 yrs. plus	16	7—43.7%	4—25.0%	5—31.2%	1
Totals	80	48—60.0%	17—21.2%	15—18.8%	4

Computation of the number of cases successfully carried through nonoperative treatment, in three age-groups (Table VII), indicates that at both extremes of life success is less apt to occur and forced operative measures are more frequent. Division of the group results in such small numbers in each subgroup that no positive statistical conclusion can be reached, and the apparent result must be accepted as being no more than suggestive. Certainly one should be particularly on the alert in children and the older patients for storm signals if conservative treatment is begun. It is interesting that of the seven children in whom expectant measures were employed, none died.

Later Course of Cases Discharged from the Hospital Without Removal of the Appendix.—The conservative treatment of appendiceal masses in other hands has followed the experience described herein; 60 per cent or more of patients admitted to the hospital can be discharged without operation.[4, 5, 6, 7, 10, 11] As already stated, the morbidity and mortality of this group resulting from retention of the damaged appendix must be charged against the method. It must be remembered, however, that a proportion of abscess cases subjected to operation (in this series 20.1 per cent) also leave the hospital carrying a diseased appendix. The disadvantage of this situation, when drainage is performed, is accepted by most surgeons as an undesirable but necessary part of an attempt to keep mortality low; and if the advantages, herein demonstrated, of conservative treatment as the preferred method are sufficiently impressive, the consequent failure to remove the appendix in the successfully treated cases must be accepted in the same sense. Just as in the case of patients discharged after drainage of abscesses without appendicectomy, all patients conservatively treated are given a date for return for interval operation, are impressed as seriously as possible with the wisdom of this measure and are warned of the necessity for immediate return in the event of acute symptoms before the interval procedure is accomplished. The

date given for return varies from six weeks to three months after discharge, depending upon the original size of the abscess and the rate of subsidence of the process under conservative treatment.

TABLE VIII

SUBSEQUENT COURSE IN ALL LIVING CASES FROM WHICH APPENDIX WAS NOT REMOVED

Subsequent Course	Interval Removal	Readmitted Acute Appendicitis	No Further Recorded Trouble	Total
Drained.....	6	5	23	34
No operation.....	14	4	32	50
Totals.....	20	9	55	84
	23.8%	10.7%	65.5%	100%

A surprising condition revealed by this study is the small proportion of patients who take this advice (Table VIII). A little over one-sixth of the patients who have had abscesses drained have returned for interval appendicectomy, and 28 per cent of those discharged after conservative treatment, a total return-rate of 23.8 per cent. Of those patients that had no operation, many more proportionally followed the surgeon's advice than of those that had been drained. The difference has no statistical significance, but it is interesting to speculate on the possibility that the unhappy hospital experience of the latter group might act as a deterrent to facing another operation. Certainly the patients treated conservatively with success, most of whom expected operation on first admission to the hospital, have no reason to fear another period of hospitalization.

Ten and seven-tenths per cent of the group discharged without appendicectomy returned with an acute attack. Three of these nine patients had allowed the new attack to progress to rupture and abscess formation. None of the group that returned died, and none were seriously ill. One patient was treated conservatively for abscess twice and, impressed by the second attack, finally returned for interval removal.

The fate of the remaining 65.5 per cent, that have not returned to the hospital, is important. Homans[12] states that roughly one-fifth of those whose abscesses have been merely drained suffer a recurrence, and Haggard[13] puts the figure at about one-half, as does Royster[14] in quoting from Reschke. About 95 per cent of all the cases included in Groups II and III are admitted to the charity service, being sent most often by their physicians from rural districts. There is no other hospital to which these patients can go in the event of serious disease. It is, therefore, a fair assumption that the great majority of these patients have had no serious attack of appendicitis. Since it is obvious that many of them have been treated so recently that there may not have been time for serious trouble to develop, the data have been divided by groups of years (Table IX).

TABLE IX

SUBSEQUENT COURSE IN ALL LIVING CASES FROM WHICH APPENDIX WAS NOT REMOVED, DIVIDED INTO YEAR-GROUPS

Year-Groups	No. of Cases	Interval Operation	Readmitted With Acute Appendicitis	No Further Recorded Trouble
1933–1934	17	2	4	11
		11.7%	23.5%	64.8%
1933–1935	25	2	6	17
		8.0%	24.0%	68.0%
1936–1937	59	18	3	38
		30.5%	5.1%	64.4%
Totals	84	20	9	55
		23.8%	10.7%	65.5%

The figures in Table IX clearly suggest, without statistical proof, that there is no striking decrease in the number that have had further trouble in the last two years over that in the earlier years. Part of this result is due to the much larger proportion of cases that have returned for interval operation during the later period. Later figures may show a number returning with acute trouble that will approach the proportion of acute readmission in the earlier period. A longer time should elapse for a larger group of cases than the number now available before a complete follow-up would be entirely useful. Since the failure to follow advice has been shown to be unexpectedly prevalent, it is planned to communicate with the entire group of appendix carriers, urging return to the hospital for appendicectomy. Possibly the development of a routine[6] by which no patient would escape repeated invitations to follow this advice would help to justify the adoption of conservative treatment. In addition it would tend to protect the patients in the drained group also from their own ignorance, fear or inertia.

The patients that have returned to the hospital for the interval removal of their appendices have spent an average of 8.1 days there. To furnish a complete picture of the economic aspect, this figure must be added to the 11.9 days (Table IV) spent during the period of conservative treatment, making a total of 20 days of hospitalization. The average stay for cases operated upon as an elective procedure is 20.7 days (Table V); but about 20 per cent of these cases must also face another hospital stay since the operation on that proportion has not included removal of the appendix. There therefore remains a slight economic advantage with the successfully treated conservative group insofar as hospital stay is concerned. The economic loss from two periods of illness is not easy to estimate. In general, the cases that leave the hospital after successful conservative treatment, however, have been ill a shorter time and are discharged in much better condition than those discharged after operation. Most of them go back to work almost immediately. Although total loss of time from work may be somewhat greater when interval appendicectomy is added to the original illness, than if operation is performed at once, the difference cannot be sufficiently great alone to determine policy.

DISCUSSION.—It is important to be certain that a suggestion to withhold operation in appendicitis be not misunderstood or adopted improperly. It need hardly be emphasized that the evidence presented has no bearing on early operation for acute appendicitis or on the expectant treatment of diffuse peritonitis. It refers only to the case in which a mass is already established. Furthermore, it offers no excuse whatever for the family physician or the surgeon to delay operation when there is no certainty that peritonitis is well localized. Finally, it is not intended to justify the nonoperative treatment even of a suitable case elsewhere than in a hospital, perhaps even than in a hospital so organized that a relatively mature resident surgeon is always available. The success herein shown, in the nonoperative treatment of abscess, must be assumed to be largely dependent on the possibility of ensuring complete general and gastro-intestinal rest, adequate maintenance of physiologic balances with frequent checks thereon, transfusions as may be indicated and, above all, close and constant observation.

During recent years a number of papers on appendicitis have presented the results of conservative treatment of an established mass.[4, 5, 6, 7, 10, 11, 15, 16, 17] The data are usually confined to mortality rates, although in a few instances the incidence of complications and the length of hospital stay have been studied. A comparison of nonoperative treatment with operative treatment of abscess in the same clinic is rare. Comparisons of figures from different clinics are deceptive, not only because of differing methods of classification but also because of different ideologic and technical approaches to the disease.[5]

All authors whose reports upon the nonoperative treatment of abscess have been reviewed in a search of the recent literature[19] have been satisfied with their results. The absolute figures for mortality agree in general with the figures presented herein; and the occasional records of the paucity of complications as well as of the surprisingly short hospital stay are also in agreement with our data. Sworn and Fitzgibbon's[11] study, especially, employing a classification of cases similar to ours and also indicating the group of cases in which conservative treatment fails, presents results convincingly parallel to ours. It may be noted that many unfavorably critical discussions of conservative treatment are based on theoretic considerations alone, presenting no data in support of arguments.[18]

As has been stated, there is some disagreement in the literature as to the condition that is treated, namely, whether or not an established abscess ever resolves spontaneously. This represents, of course, an unimportant distinction. The essential element is the localized mass following appendicitis for which conservative treatment is proposed, a mass which may or may not contain pus. The problem to be settled is whether such a mass is better treated by or without operation.

This study was undertaken, as has been said, to appraise the results of a method of treatment adopted on a clinical basis. The University of Virginia Hospital surgical staff is unanimous in the opinion that the data here presented

justify the continuation of this method under the local conditions. Success has been shown to be far greater than had been anticipated. It is felt that any case of appendicitis, at any age, which presents a mass is best handled by initiating expectant treatment in the absence of definite, immediate surgical indications; and that such treatment should continue so long as improvement continues. The sicker cases, that do badly without operation, probably belong to the type that would do badly with operation. The type that has shown adequate resistance to the infection clearly seems to have had a remarkably easier and less dangerous experience in our material when operation was withheld, than when operation was performed under what we used to consider favorable conditions. A paragraph from Love[4] may well be quoted: "I feel sure that psychological reasons are a great deterrent to the adoption of expectant treatment. If a case treated on delayed lines ends fatally it is usually regarded as a tragedy, and all concerned may have lingering doubts in their minds as to whether immediate operation would have saved the patient. On the other hand, if the appendix is immediately removed and the patient succumbs, the general impression is that because immediate operation was performed everything possible was done, and the fatality is accepted philosophically."

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DISCUSSION.—DR. FREDERICK A. COLLER (Ann Arbor, Mich.): This paper has been most instructive to me, emphasizing as it does the value of the conservative treatment of abscesses, a point of view I have been approaching perhaps too slowly.

The outstanding fact about appendicitis is the importance of removing the appendix early, while the infection is confined to the appendix or its vicinity. Our main efforts should be expended toward bringing about this ideal treatment. Unfortunately, we are called upon to treat the results of neglected cases or of poor treatment that result in diffuse peritonitis or abscess formation. There is a diversity of opinion on the proper method of handling these two complications. I think everyone now admits the importance of deferring operation long enough to restore the biochemical balance of the patient. After this has been effected, many surgeons insist upon the immediate removal of the appendix or drainage of the abscess. Others continue the Ochsner regimen, deferring operation until indications arise.

In our clinic, for ten years, we have used the conservative method in the treatment of peritonitis, operating only if the patient does not improve or if the abscess develops. In patients who come to the hospital with abscesses, we have usually drained the abscess after restoring the patient's biochemical balance. During the past three years, we have been observing these patients with abscess for a longer time before operation, largely as a reflection of our conservative attitude toward peritonitis rather than due to any definite intellectual effort.

About 60 per cent of the patients with peritonitis treated by the deferred operative method develop abscesses. These abscesses are often large, filling the pelvis and bulging into the rectum or the lateral gutters, and we feel from our experience that these should be drained when their presence is obvious. We have lost several patients in whom drainage of these large collections of pus was carried out too late.

With the feasibility of conservative treatment of the mass around the appendix, be it single or multiple abscesses, or infiltrated omentum or intestine, I am in accord, due to our own small experience and to the observations of Doctor Lehman, and in this group, I propose to carry out the conservative treatment more as he has outlined. I do think, however, we should draw a distinction between the large collections of pus resulting from the Ochsner treatment of diffuse peritonitis, and the well localized mass around the appendix, called an appendix abscess. The collection of pus should be drained. We urge the subsequent removal of all appendices that have been the cause of peritonitis or abscess.

During the past four years, we have treated 574 patients with acute appendicitis and its complications, with a mortality of 1.9 per cent. Of these, 496 had the disease limited to the appendix or its vicinity and these were treated without a death. There were 32 patients with diffuse peritonitis, with a mortality of eight, or 25 per cent. Of those dying, two were severe diabetics and one patient was moribund on admission. Forty-six patients were admitted with abscesses and all but one were operated upon during their

stay. Half of these were operated upon as soon as their general condition was satisfactory, usually within 24 hours. The other half were operated upon in an average of one week after admission. Three patients died, two of peritonitis and one of pneumonia. It is possible that deferring operation longer might have led to a happier result.

There is one great drawback to advocating any type of delay in the operative treatment of the complications of appendicitis. It requires an effort of mind and the possession of surgical judgment; these are not always available. The bare mention of conservatism in any connection with appendicitis is often misconstrued to mean medical treatment for all appendicitis.

DR. J. SHELTON HORSLEY (Richmond, Va.): Doctor Lehman's analysis of his cases is extremely interesting. I have followed, during the last seven years, a somewhat different course of treatment. It is necessary to have a basis for statistics of appendicitis, and that basis should be that every case of appendicitis treated, no matter by what means, must be included in the mortality rate. A patient is just as dead who dies following the Ochsner treatment as one who dies after an operation.

When you begin to split very fine clinical and pathologic hairs as to the difference in a stage of appendiceal inflammation, you are running into a great source of potential error. Of course, with very excellent experience and good surgical judgment such as Doctor Lehman has, you can reduce the errors to a minimum, but one still has a potential field for them, no matter how careful one may be.

During the past seven years, the surgical staff of St. Elizabeth's Hospital, consisting of my two sons and myself, have adopted a general standard, which has proven quite satisfactory, partly because it is simple. There have been three features which we have been using for a long time: Immediate operation in all cases of acute appendicitis, the McBurney incision, and simple ligation of the stump of the appendix; but beginning about seven years ago, we combined five different features which I shall speak of later.

TABLE I

DEATH RATE FROM APPENDICITIS PER 100,000 POPULATION IN VIRGINIA

Year	Deaths	Percentage per 100,000
1913	137	6.4
1920	194	8.4
1925	260	11.0
1930	267	11.0
1935	247	10.1

The highest death rate since 1913 was 12.9 per cent, in 1932.

Table I shows the incidence of deaths from appendicitis. As is well known, this death rate is increasing, at least it has been for the last 20 years. Whether this is due to conservative treatment, to "freezing" it out, or to waiting, I do not know, but it just happens to come along that way while these procedures seem popular. In Virginia, deaths show a very distinct rise from 6.4 per 100,000, in 1913, to 10.1 per 100,000, in 1935. The highest death rate since 1913 was 12.9 per cent, in 1932.

TABLE II

APPENDICECTOMIES AS THE MAIN PROCEDURE PERFORMED AT ST. ELIZABETH'S HOSPITAL

(January 1, 1931, to January 1, 1938)

	Cases	Deaths	Percentage
Acute appendicitis	494	3	0.607
Acute appendicitis with peritonitis	100	2	2.0
Subacute and chronic appendicitis	200	0	0
Carcinoma of appendix	1	0	0
	795	5	0.6

Table II represents our own statistics from January 1, 1931, to 1938, and I may say that we have had no deaths this year so far. We have tried to adopt a simple method of classifying the cases. We have what we call acute appendicitis, 494 cases with three deaths. We have acute appendicitis with peritonitis, in which we include, to make it as simple as possible, abscesses and spreading peritonitis as well, and in which we have 100 cases with two deaths. We have had 200 cases of subacute and chronic appendicitis, and one carcinoma of the appendix, with no deaths.

Of the five deaths, two were neglected cases when first seen. There was gangrenous bowel, which had to be resected at the time of operation, in one case, and an abscess of the tube on the left side which so involved the bowel that it had to be resected in another case. Then there was a patient, age 72, who had a retrocecal appendiceal abscess, that had been present for some weeks and which we thought was cancer of the cecum. The appendix was removed and the abscess drained. During convalescence, he developed a decompensating heart and pulmonary edema and died four days after operation. The fourth death was that of a man, age 50, who had a gangrenous appendix removed without draining and made a satisfactory recovery except for a fibrinous pleurisy, right side, ten days after the operation. That cleared up and the patient was about ready to leave the hospital when he died of a pulmonary embolus. The fifth death was in a very obese, alcoholic male, who developed paralytic ileus and uremia and died on the sixth day after the operation. Necropsy showed no peritonitis.

The routine procedures at our clinic are:

(1) Immediate operation for acute appendicitis, as soon as the diagnosis is made, no matter what the stage of the disease.

(2) McBurney incision, gentle handling of the tissues, and always removal of the appendix. Removal of the appendix obviously saves morbidity and hospital expense, and reduces the mortality rate.

(3) Suction apparatus instead of sponging. Sponging presses sepsis into the areolar tissue. That is a very important point in technic. If you sponge the pus out with gauze on a sponge holder, you get out some pus but you also massage into the retroperitoneal tissues some of it.

(4) Physiologic rest of the affected colon and cecum, by avoiding proctoclysis and by administering intravenous dextrose or dextrose in salt solution or Ringer's solution, and using a Jutte or Levine tube in the stomach; also using a minimum of drainage. Physiologic rest is what we want, and by giving proctoclysis you are doing exactly the opposite thing. You are pouring into the colon and cecum, fluid which not only distends the bowel and tends to create peristalsis, but also increases the absorption from that region, because the right side of the bowel is the chief absorptive area for

fluids. In other words, you are working just as hard as you can, tissue that should be rested.

(5) The simple treatment of the stump of the appendix, merely ligating and bringing over a tag of peritoneum-covered fat to protect the stump from the drainage tube.

In every acute case, abscess or not, we operate at once and always remove the appendix. We have not failed to remove the appendix in a single one of these cases. But you should not do that unless you follow all five of those points.

H. E. Robertson, of the Mayo Clinic, has called attention to the fact that in every instance in which the appendix was removed, incidental to some other operation, and the patient died of something else, up to 21 days, he found a pocket of pus where the appendix stump had been buried. Simply tie a ligature around it, not clamping it, because that injures the tissues unnecessarily, just tying it tightly enough to cut through the mucosa, and let it roll up, cut off the appendix with an electric cautery, and disinfect the stump with carbolic. A tag of fat may be brought over by the ends of the ligature on the stump.

Let me repeat again that we have been doing all of these things for only seven years. We had been using McBurney's incision before for many years, but unless you are going to give the tissues physiologic rest, unless you are going to use a suction apparatus and not force the pus into the retroperitoneal tissue, unless you are going to treat the stump of the appendix simply, these other things such as immediate operation and always removing the appendix should not be performed.

Dr. Thomas G. Orr (Kansas City, Kans.): I have been very much interested in this report because we have been practicing practically the same method during the past three years. Any patient admitted to the hospital with a mass in the lower right quadrant of the abdomen, we allow to wait until we are sure that the mass is going to develop into a full-blown abscess before recommending drainage. About 50 per cent of our cases get well and go home without any operation. We are very careful to warn them to return at the end of three months for an interval appendicectomy. It is true that some of them will not come back, notwithstanding they have been advised it is their responsibility. Occasionally they return with another acute attack. We have had this happen in a number of instances, but do not consider that there is any more danger involved than that which attended their first attack.

There have been many different published ideas concerning the treatment of appendicitis. I had occasion a short time ago to review 12 different recent articles on the statistics of appendicitis with peritonitis, and I was surprised to find that the death rate varied from 1.43 up to 52 per cent. There is either a great deal of difference in appendices or there is something wrong with statistics.

We divide our cases into four groups: Those in which the disease is confined to the appendix, and those that have ruptured and have no distention, are operated upon at once. I believe distention is the crux of the whole situation. Those patients without distention who are operated upon and have their appendices removed have a very low death rate. The third group are those with masses in the right lower abdomen, which we allow to wait. We also postpone operation in the fourth group having general peritonitis.

After perforation and operation, an abscess occasionally develops in the pelvis. A large percentage of those masses will resolve without operation if given sufficient time.

DR. ROSCOE R. GRAHAM (Toronto, Can.): I would like to express my personal thanks to Doctor Lehman for classifying the way in which he is studying appendicitis.

One is lulled into a very false sense of security by a mortality of 3 per cent. We have that; but at the same time, one analyzes the group in which the death occurs, as in the case that is perforated. I have very little interest in reading a report on the treatment of appendicitis in which they have not very sharply differentiated perforated from nonperforated groups.

In December, 1929, we lost two cases which presented masses, that were operated upon precipitately, without correction of the biochemical fault. They both died of colonic bacteriemia. We looked up our mortality on cases presenting masses, and it was 22 per cent. We looked up our mortality on cases of perforated appendicitis, and it was 17 per cent. The comment that was made to us was that we had better learn how to operate on appendicitis. I do not believe that is the point. I think that our management coincides very closely with Doctor Lehman's.

There are two points I would like to make: First, there are some people who are desperately ill and, as in some cases of perforated duodenal ulcer, one has been in error in determining why they are ill. They are ill because of the biochemical balance that Doctor Coller has mentioned. The patient comes in with a temperature of 105° F., cold to his elbows and cold to his knees, and a mass in the right iliac fossa. That patient, when he has had his biochemical balance restored, is an unbelievable picture after 24 hours, if you have not experienced it.

Sixty per cent of our cases have been discharged without operation. We explain their responsibility and a very small percentage have not returned in three months. Second, when you have full-blown abscess in the right lower quadrant, you are not operating for appendicitis. You are operating for an intraperitoneal abscess and that is the same as an abscess any place else. That means drainage.

DR. OWEN H. WANGENSTEEN (Minneapolis, Minn.): The method of treatment which Doctor Lehman has described has been a matter of routine in the surgical clinic at the University of Minnesota since 1931—a preliminary period of trial extending back to 1929. Since 1931, no appendiceal abscess has been operated upon primarily in our hospital. Such cases are treated conservatively by the employment of suction applied to an inlying duodenal tube, even in the absence of distention, and by the administration of paraoral fluids.

I should like to offer a word of caution, however, concerning prolonged, expectant treatment in the patient with a very large abscess or rather in the patient whose abscess continues to be large. As Doctor Lehman pointed out, a surprisingly large number of abscesses resorb completely without operative intervention—the patient then comes back for appendicectomy in the interval. If, however, a large abscess gives little evidence of resorption over a short period of observation, it should be incised. For, apart from the possibility of intraperitoneal extension of the abscess by rupture, there is another hazard in large abscesses, namely, burrowing of the abscess into the mesentery with erosion of a blood vessel. I have seen this complication, and as you can well believe, it is a disastrous occurrence.

Subsidence of fever and *decrease* in the size of the abscess are the signs which indicate that it is safe to pursue a conservative regimen. If fever continues unabated and a large abscess fails to diminish in size, incision and drainage are indicated.

The advent of continuous gastric siphonage has, of course, extended the conservative plan of treating appendiceal abscesses outlined by the late A. J. Ochsner many years ago. I subscribe fully to what Doctor Horsley said concerning the avoidance of enemata. Evacuant enemata, as well as the administration of a barium enema for purposes of diagnosis, are hazardous in the presence of intraperitoneal suppuration. Many lives will be saved if house officers are instructed never to administer enemata when intraperitoneal suppuration is present or suspected.

Dr. Allen O. Whipple (New York City, N. Y.): With all the emphasis that has been laid upon the conservative treatment of peritoneal abscess, we have got to bear in mind the effect it has upon the general practitioner. During the past year, I have seen four patients, who have come in with either peritonitis or peritoneal abscess, and the reason the doctor gave was that he had read a good deal of literature recently about conservative treatment of appendicitis.

There is a danger we must bear in mind, if we continue to emphasize the conservative treatment. This is misunderstood by a great many of the general practitioners, who will find more advantage in treating their cases of appendicitis conservatively instead of having the cases operated upon during the time when the mortality, as is shown by two opposite methods of treatment, is exceedingly low.

Dr. Howard Lilienthal (New York City, N. Y.): What we should do is to try to influence the general practitioner so that not he, but the surgeon, shall decide whether or not an operation shall be performed. Surgery is not, strictly speaking, a science; it is only partly a science.

The most arresting part of this paper appears to me to be the urgent advice that practitioners of medicine should not take the responsibility of treating appendicitis without surgical counsel. After all, to call in a surgeon does not mean that an operation is inescapable. It simply means that the medical man will be reinforced by a surgical opinion. And that this will influence, but not necessarily persuade, the practitioner. This aspect of the subject should be frequently presented in medical literature.

Dr. Edwin M. Miller (Chicago, Ill.): I have been intensely interested for several years in the treatment of the type of case that Doctor Lehman has presented, and I have taken even a more conservative attitude than he seems to have followed. Ordinarily, these cases form a well recognized, clearly defined group, but, on the other hand, there is the occasional case where one is in doubt, even after a most careful examination, as to whether it falls into Group II or in one of the others.

When there is that matter of doubt, it may be cleared up by relaxing the patient very thoroughly under anesthesia. I have had the experience of having found a definitely palpable mass under anesthesia and leaving it alone. I have gone even further, and have opened the abdomen in an indefinite case and then have found a localized mass with the abdomen open, and left it alone.

I wish also to say that not every localized palpable mass, in a patient who gives a history which simulates that of a preceding acute attack of appendicitis, is the result of perforation of an appendix. I have had the experience of seeing a case where this was suspected, only to find upon entering the abdomen, not an appendiceal mass but an irreducible intussusception in which there had been an atypical history and atypical physical findings.

Not only that, but many of these localized, palpable masses do not occupy the right lower quadrant of the abdomen. Many times in our experience they have occupied the lower left quadrant and not infrequently, as has been said, they are confined to the pelvis.

DR. FRANZ TOREK (Montclair, N. J.): I want to confine my remarks to one class of cases, namely, those with diffuse suppurative peritonitis. By "diffuse" I mean those that have extended well over to the left side, with free pus not only in the region of the perforated appendix but also in the pelvis and well over to the left side.

Those are rarely seen now, but between 30 and 40 years ago they were not rare. I reported on these cases in two publications, each covering 18 cases, so that, by 1908, I had recorded 36 cases with diffuse suppurative peritonitis. I mention them now because the way in which I treated them may perhaps be new to some of you.

The treatment consisted in a median incision from the pubis up to at least two inches above the umbilicus, letting the pus flow out through the wound, removing the appendix as quickly as possible, and then washing the entire peritoneal cavity with hot saline solution, first pouring it into the right side where the appendix was, then in the pelvis, then in the left side, and, if necessary, also higher up. The washing was accomplished by pouring from a flask or a pitcher and using the gloved hand to move the intestines from side to side, in order to reach all the places where pus might be found.

By 1908, as I say, I had operated upon 36 cases, but since then I have had only four cases, which is a proof that the diagnosis of appendicitis has been so much improved these later years that the extensively diffused cases of peritonitis are rarely seen.

An important thing is that in those cases, I did not drain. You may drain an abscess, and it ought to be drained, but if you have to deal with a diffuse peritoneal involvement, you had better make up your mind that it is impossible to drain the whole peritoneal cavity. The washing, therefore, had to be so thorough that the water finally ran back absolutely clear. The abdomen was closed without drainage. Only in a few cases in which I saw that the cecum was so nearly gangrenous that it was bound to perforate, did I insert a drain through a separate opening down to it. In those cases, after some time, pus and feces came out through the drain.

Another point is the closure of the wound. The incision was closed by simply taking through-and-through sutures without any attempt to coapt the separate layers. I did this in my first case, who was so extremely weak that I thought she would die soon after I got through, and that I must make haste to avoid having the patient die on the operating table. She, however, recovered, and since then I have continued to employ that same method of suture in all the cases of diffuse suppurative peritonitis.

The reason why I did not return to the customary suture, in layers, was to avoid spreading infection from the incision to freshly exposed muscle and fascia, as these tissues are not nearly as capable to resist infection as the peritoneum is.

The cases that I reported totaled 36, and there were six deaths. In the four subsequent ones, no deaths. So I had six deaths in 40 cases, a mortality of 15 per cent.

DR. EDWIN P. LEHMAN (closing): I agree entirely with Doctor Coller in relation to the large abscesses. I have not had the experience that Doctor

Wangensteen reports, of rupture into a blood vessel, but I presume if we continue with this treatment, such an event may occur.

We believe that most of the large abscesses will do well with at least some delay in operation. In most instances a delay of three or four days will place the patient in considerably better condition for operation.

I know no statistics on appendicitis that are as good as those that have been presented by Doctor Horsley. Of course, as Doctor Coller has pointed out, the difficulty of comparison between clinics is very great. When Doctor Horsley was to present these statistics at our state meeting last fall, I looked up a group, approximately the size of the group that he has reported, limited to private cases, and I found that our mortality in the private group was not appreciably greater than that of the group he has presented.

We also have had the experience of having masses palpable by rectum disappear without operation in the same way that Doctor Orr reports.

We realize the danger of misconstruction of a proposal for conservative treatment in any phase of appendicitis and have, therefore, placed in a prominent position in the text of the present communication a clearly outlined statement of the type of case to which this treatment is limited, namely, the case with a demonstrable mass.

I agree that there is danger of missed diagnoses, and I presume also that they will be embraced in our experience. So far, we do not know of any diagnoses that have been missed by this method of treatment.

REGIONAL ENTERITIS

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REGIONAL enteritis, terminal ileitis, or nonspecific granuloma of the intestine is either occurring more frequently or is being recognized more often than in the past. A study of the literature on nonmalignant disease of the intestine gives the impression that many such lesions have been incorrectly diagnosed as tuberculosis.

Inflammatory intestinal lesions were recognized many decades ago. In 1806, a case was reported by Combe and Saunders in which three feet (90 cm.) of the terminal ileum was involved. The description of this condition and the specimen strongly suggested that the process was nonspecific. In 1844, Abercrombie reported a lesion in the intestine of a child, age 13, which was apparently one of nonspecific ileitis. Another case of a similar nature was described by Braun, in 1909. The 14 cases reported by Crohn, Ginsberg and Oppenheimer, in 1932, gave the first classic description of what is known as "ileitis," "granuloma of the intestine," or "segmental enteritis." Others who have described inflammatory disease of the intestine are Tietze, Moschowitz, and Wilensky and Mock.

TABLE I

REGIONAL ENTERITIS

Brown and Pemberton's Series of 39 Cases

No. of cases	Segment Involved	Surgical Procedure	Results
2.....	Entire jejunum (1) Upper jejunum (1)	Exploration	Died 7 mos. later
13.....	Ileum (1 to 8 segments)	Ileocolostomy	2 apparently well 11 slightly improved
2.....	Ileum and transverse colon	Ileosigmoidostomy	1 slightly improved 1 died 6 mos. later
20.....	Ileum (17). Ileum and cecum (3)	Resection of ileum and cecum	16 well (2 to 6 yrs.) 2 died later (cause unknown). 2 died postoperatively
2.....	Ileum and cecum (with fistula and abscess)	Drainage of abscess in right lower abdominal quadrant	Not traced

At the Mayo Clinic, several cases of so-called terminal ileitis have been observed in which the cecum and portions of the large intestine were also involved. In Crohn's original article he expressed the belief that this disease was confined to the ileum, but, in 1936, he and Rosenak reported a total of 60 cases, confirmed at operation, in nine of which there was involvement of some

portion of the colon. Colp reported a case in which not only the terminal ileum but the cecum was also involved.

In 1937, Pemberton and Brown collected 39 cases of nonspecific inflammatory disease of the intestine from the records of the Mayo Clinic. In 36 of these cases the diagnosis was substantiated at operation (Table I). Since then 30 additional cases have been encountered at the clinic, which form the basis of the present report. Twenty-one of these 30 patients were seen during a period of nine months. It seems logical to infer from this, therefore, that the condition is occurring, or is being recognized, with greater frequency than previously.

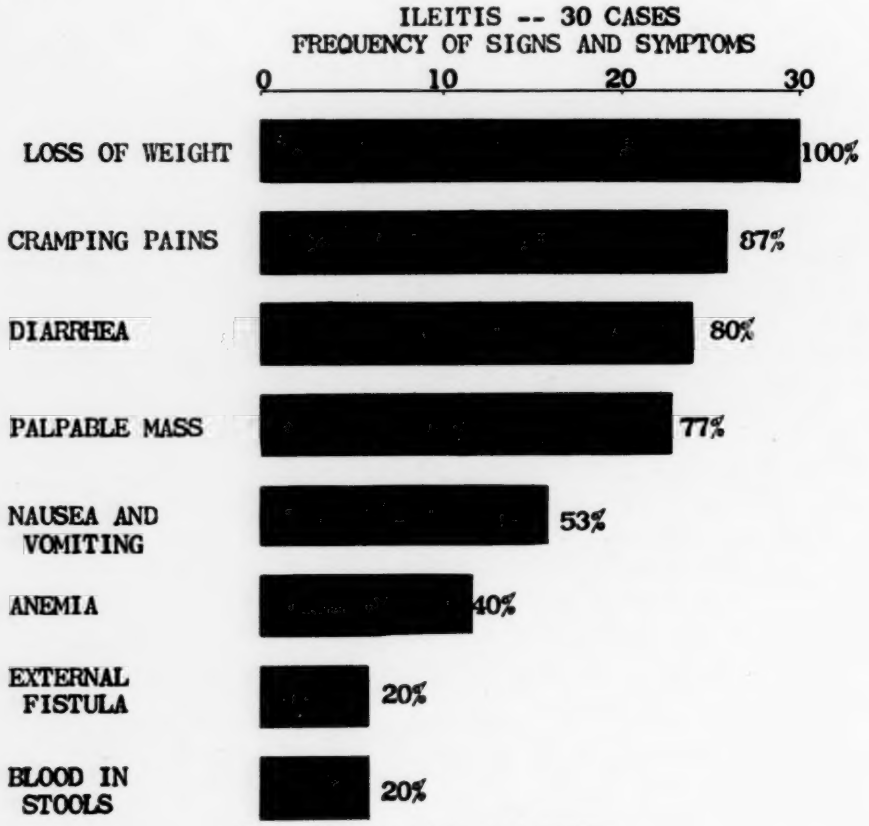

FIG. 1.—Frequency of signs and symptoms.

Figure 1 graphically represents the signs and symptoms of the disease from the standpoint of frequency. The chief subjective symptoms were intermittent cramping pain and diarrhea. In each of the 30 cases there had been a moderate to marked loss of body weight. The clinical history would lead one to believe that this reduction in weight was due to the patients' fear of eating rather than to the disease itself since the majority of them complained of cramps and pain soon after the ingestion of food. On physical examination

a mass was present either in the pelvis or right lower abdominal quadrant in all except seven of the 30 cases. The rope-like character of the lesion was often manifest as a firm sausage-shaped tumor. In 16 cases there was a history of nausea and vomiting.

Marked anemia is frequently associated with disease, and particularly carcinoma, of the ileocecal region, but in these 30 cases of regional enteritis, anemia was present in only 12, and then only to a moderate degree, even though the enteric disease in some instances involved both the cecum and terminal ileum. The leukocyte count as a rule was slightly increased. Six patients gave a history of having passed blood by rectum; bleeding probably occurs more often in association with nonspecific enteritis than this statement would indicate, but is not noticed. A fistula of the external type was present in six cases, in three instances operation having been performed following a diagnosis of acute appendicitis. In some of the instances in which there had been a previous operation, mention of an indurated cecum or plastic exudate over the surface of the terminal ileum was made. In three cases fistulae of the internal type were present; one patient had a fistula between the ileum and urinary bladder and two a fistula between the ileum and lower part of the sigmoid.

In 23 cases, there was a definite history of remission of symptoms lasting from two to four weeks. Previous treatment had been instituted in 22 of the 30 cases; 13 patients had undergone appendicectomy, and nine had been treated on the assumption that their difficulty was amebic dysentery.

The clinical history in each of these 30 cases strongly suggested regional enteritis and in each case this suspicion was substantiated roentgenologically. None of the patients had a history suggestive of active pulmonary tuberculosis and, roentgenologically, there was no evidence of pulmonary disease.

Surgical treatment was undertaken in all of the 30 cases. Single stage resection was performed in ten cases, ileocolostomy with subsequent resection in ten, and ileocolostomy alone in the remaining ten. In those cases in which ileocolostomy was the only surgical procedure, the patients were advised to return for resection of the diseased segment of bowel, but possibly because of improvement, they have not complied up to this date. It is of interest that all except three of these ten patients have the same symptoms as before surgical intervention but to a lesser degree. Eight of them have gained 15 to 20 pounds (6.8 to 9 Kg.). In the 20 cases in which single or two stage resection was employed, all symptoms completely subsided except in four cases in which a slight tendency to diarrhea remained (four to six stools daily).

In this series of 30 cases, upon whom 40 operations were performed, there were four deaths: one from pulmonary embolism, one from peritonitis, one from obstruction, and one from pneumonia. The fact that there was but a single death following the ten primary resections might lend credence to the belief that this procedure should be employed more often. My reason for performing primary resection in this group of cases was either that the patient appeared to be in good condition or that multiple external fistulae were pres-

ent. In the latter instance many loops of intestine were found to be adherent in the right iliac fossa and, in order to become properly oriented in performing the operation, it was necessary, in my judgment, to mobilize the coils of intestine in this region en masse, which made a single stage resection imperative. In all cases of resection a temporary stoma of the Witzel type was established at a point in the ileum about 24 to 30 inches (60 to 75 cm.) proximal to the anastomosis. This procedure has proved of great value in preventing distention due to the accumulation of intestinal gases. The enterostomy tube is removed as a rule on the twelfth postoperative day and this is followed by spontaneous closure.

It is my impression that, in its earliest stage, regional enteritis consists of enlargement of the mesenteric lymph nodes and ulceration of the mucosa. Brief mention of two cases will tend to substantiate this opinion:

Case 1.—Female, age 29, came to the clinic because of intermittent attacks of severe cramping pain in the right lower abdominal quadrant. These attacks had begun two months previously. Her family physician, who had been in attendance during many of the attacks, reported having found moderate tenderness in the right lower quadrant, moderate elevation of the leukocyte count, a temperature of 102° F., and diarrhea consisting of three to five stools per day, unaccompanied by the presence of blood. At the clinic, physical and laboratory examinations failed to reveal evidence of the disease, the patient apparently being in a period of remission. Roentgenologic studies of the gastrointestinal tract, however, revealed a defect in the terminal ileum.

Operation.—On opening the abdomen no abnormality could be detected in the terminal portion of the ileum. The small intestine and colon were then examined carefully but the lesion described by the roentgenologist could not be found. The lymph nodes adjacent to the terminal portion of the ileum were slightly enlarged. Two months after this exploratory operation the attacks recurred with increasing severity, and three months after the surgical intervention a second operation was undertaken, at which the distal portion of the ileum was found to be markedly thickened and covered by a thick, grayish, plastic exudate. One stage resection was performed and satisfactory recovery followed.

Case 2.—Female, age 24, came to the clinic complaining of diarrhea, fever and acute abdominal pain which had occurred intermittently during the preceding six weeks; however, she had not consulted a physician. Physical examination revealed no abnormal finding. Other investigations did not show anything significant except that the roentgenologist reported the presence of a filling defect in the terminal portion of the ileum. At operation, however, careful examination of the small intestine and cecum did not reveal the presence of a tumor or other abnormality. The patient succumbed to pneumonia 12 days postoperatively. At necropsy, the terminal ileum was grossly normal, but when the intestine was opened an ulceration 5 cm. in diameter was found.

The question is: Should not these two cases be classified as instances of early regional enteritis or terminal ileitis?

In a third and similar case, in which there was no evidence of disease of the terminal portion of the ileum by direct visualization or palpation, the ileum was transilluminated by the use of a Cameron cold light, which was placed along the lateral surface of the intestine. Such lesions as ulcerations or polypi can be visualized quite clearly in this manner, when by such measures as palpation no abnormality can be detected; further use of transillumina-

tion is suggested as an aid in determining the presence or absence of lesions in hollow abdominal organs.

An analysis of the entire series of 69 proved cases of regional enteritis, in which the diagnosis was made and the patients were treated at the clinic, would lead one to the inevitable conclusion that the treatment of choice is radical removal of the involved intestine (Table II).

TABLE II

SURGICAL RESULTS IN 69 CASES OF REGIONAL ENTERITIS

No. of Cases	Surgical Procedure	Results
25.....	Ileocolostomy	5 well, or have only mild symptoms 20 obtained slight or no improvement, or were worse
40.....	Resection	4 died postoperatively. 2 died after dismissal (cause unknown). 34 well 6 mos. to 6 yrs.
2.....	Closed as exploration (condition too extensive for resection)	Died 7 mos. postoperatively
2.....	Drainage of abscess	Fistula 8 mos. later. Fistula 1 yr. later
Total 69		

Cases have been reported in which spontaneous cure evidently occurred without resection; for example: A colleague informed me recently of an operation undertaken upon a young woman for the purpose of removing an acutely diseased appendix. Exploration revealed a so-called chronic appendix. Appendicectomy was performed. In the terminal ileum, about 10 cm. from the ileocecal juncture, there was a definite thickened area covered by a thick, gray, plastic exudate. The process apparently involved the entire circumference of the ileum. The mesentery adjacent to the segment of diseased bowel contained many enlarged nodes. Omentum was used to cover the affected portion of ileum and the abdomen was closed. Nine months have passed since appendicectomy was performed in this case and meanwhile the symptoms have gradually subsided. This case is mentioned as an example of the exception rather than the rule.

Segmental enteritis is an inflammatory disease which has great tendency to progress, as is evinced by the fact that unless radical excision is employed, further spread of the process occurs, often involving the site of an anastomosis and thus necessitating another radical procedure. Several such cases have been reported. A case in point is appended:

Case Report.—Female, age 12, was admitted to the clinic because of an illness of two and one-half years' duration, which was characterized by fever, chills, cramping lower abdominal pain, diarrhea and vomiting. For periods of a month or more the child was without symptoms. Her growth had apparently been markedly impaired. Examination revealed the presence of a diseased terminal ileum; the defect appeared

roentgenologically to involve about 30 cm. of the intestine. Ileocolostomy was performed and the patient was advised to return in three months for resection of the diseased intestinal segment. Following the short-circuiting operation the symptoms decreased in severity and there was a marked gain in weight. Fourteen months after ileocolostomy the patient returned for reexamination. She appeared to be in good health. Meanwhile the stools had been loose occasionally but only mild attacks of cramping lower abdominal pain had occurred intermittently. At this time the defect in the terminal portion of the ileum appeared roentgenologically to be more extensive than at the previous visit. The mother of the child refused to have surgical intervention undertaken.

Experience in similar cases would lead one to believe that this patient will in the near future have symptoms of obstruction because of encroachment of the progressive inflammatory process on the ileocolonic stoma.

The cause of regional enteritis has not yet been explained. Some observers are inclined to think that an allergic tendency is responsible for it. Bohn has reported a case which is suggestive: A boy, age 9, complained of symptoms such as frequently accompany regional enteritis. He was hospitalized and given a liquid diet. Each afternoon his temperature became elevated to from 103° to 105° F. By a process of elimination it was discovered that when milk was not present in his diet, his temperature was not above 99° or 100° F., but that when the use of milk was resumed there was marked elevation of the temperature and associated cramping pain of much more violent character than during the period when milk was excluded. This case is at least interesting.

The consensus at present seems to place the cause of regional enteritis on an infectious basis. Pumphrey, however, has studied the enlarged lymph nodes as well as the segments of diseased bowel removed in many of the cases mentioned in this report. First, he attempted to prove the presence or absence of tubercle bacilli. Guinea-pigs were inoculated but none of them developed tuberculosis. Cultures were taken, using various media, but he was unable to detect any constancy of organisms. Many of the organisms that were recovered were cross-agglutinated with the patient's serum, but positive results were not obtained. Organisms recovered from the diseased intestinal wall and from the enlarged lymph nodes were injected intravenously into rabbits without producing visible lesions. Attempts were made to culture fungi from the lymph nodes and the affected tissues in three cases but the presence of pathogenic fungi could not be demonstrated.

SUMMARY AND CONCLUSIONS

A total of 69 patients with regional enteritis have been treated at the clinic.

Regional enteritis is apparently increasing in frequency, or the disease is being recognized more often than formerly.

Rational treatment at the present consists in resection of the diseased segment of intestine. A short-circuiting operation such as iloecolostomy often affords temporary relief and apparently, in isolated instances, the procedure may produce subsidence of all symptoms. A two stage operation seems the

procedure of choice. So-called spontaneous cures, however, are occasionally recorded.

Ulceration of the mucosa and enlargement of the mesenteric lymph nodes may be the beginning of regional enteritis, and transillumination of the intestine may prove to be an aid in locating such early lesions.

The etiology of regional enteritis is unknown. Studies of specimens which have been removed have failed to reveal a specific Bacterium as the cause of the disease. A case is mentioned in which an allergic phenomenon was recorded.

DISCUSSION.—DR. HORACE BINNEY (Boston, Mass): I do not feel that I can discuss the subject as a whole, which Doctor Dixon has presented so interestingly, because my experience is quite limited. However, as concerns the treatment, I think it would be of interest to present to you a case in which I carried out a procedure which perhaps is not according to Hoyle, but which, under the circumstances, seemed to be the best thing to do and the result seems to indicate that I used correct judgment in employing it.

The patient was a boy, age 19, who, four years ago, came under my care, with the usual history of attacks of appendicitis, the earlier ones subsiding and then having an appendicectomy, followed by the formation of a fecal fistula in the scar. That was operated upon but the fistula broke out again. He came then under my care again. I felt it probably was a case of tuberculosis of the idiocecal region. At that time he had a fistula, a palpable mass, and some obstructive symptoms—a griping pain, *etc.* I did not know then about the string sign, and our only roentgenologic evidence was that the fistula had communicated with the cecum.

At operation, I developed this much thickened and enlarged cecum and determined upon its removal, probably with an anastomosis of the ileum to the transverse colon, but in removing the cecal portion, which was very adherent, I broke through an ulcerated area and into the intestine. That left me with an infected field in which to work. The lower ileum was somewhat thickened and enlarged but it was smooth and there was no external evidence of any ulceration or fistulous formation in that region. The specimen when removed showed a very irregular, enlarged, and thickened cecum and a small portion of ileum.

Rather than risk infecting the general peritoneal cavity by performing an ileotransverse colostomy, I was able to effect an end-to-end anastomosis, leaving an indefinite amount of somewhat thickened but dilated lower ileum. The patient made a perfectly good recovery and was discharged the third week. Subsequent roentgenograms show a normally functioning bowel.

The patient, during the past four years, has been perfectly well and has gained 50 pounds in weight. I think the result shows that I was justified in leaving a suspicious portion of the lower ileum, although I do not pretend to say that that is a correct procedure as a general rule. I feel that, as Doctor Dixon says, the proper procedure is a complete resection in either one or two stages, when feasible.

DR. EDWIN P. LEHMAN (University, Va.): One of the most useful things that Crohn did in his first communication on this subject was to divide the disease into four pathologic stages. Interest, as far as the surgical treatment is concerned, has, of course, been largely directed to the later stages of the disease. I have recently reviewed the literature in relation to the first or acute

phase. There seems to be a good deal of difference of opinion as to whether or not the acute phase should be treated by radical operation.

I am reporting (Review of Gastro-Enterology) a group of seven cases, seen at the onset of symptoms, all of them explored under the diagnosis of appendicitis, except one case that had had the appendix removed previously. They were all treated with nothing more radical than appendicectomy, which was performed not with the idea of curing the disease, but because the appendix was readily accessible. Of these seven cases, two have been completely symptom-free for nine and one-half years. One has been completely symptom-free for four years. One has been symptom-free for a year, and in a recent check-up complete clinical and roentgenologic studies revealed no disease.

It has seemed to me, on the basis of this experience, that the first attack is probably not the time to perform a radical operation. Some of these cases will undoubtedly resolve. It is a good deal safer at the first attack of symptoms, in the acute stage, to perform no surgery except that which is required for diagnosis, and possibly an appendicectomy, so long as the latter is easy to do. Radical surgery can follow, if simple exploration is not followed by resolution. Such a course makes obligatory very careful observation of the patient after the exploratory operation.

Dr. Harry H. Kerr (Washington, D. C.): I would like to ask Doctor Dixon if they have had any recurrences, in their experience, in the large group of cases he reported. I have recently had one that was quite illuminating, and Doctor Shearer of Washington has reported three recurrences with three resections in one case. The patient is now well.

The instance personally observed occurred in a woman who had lost some 60 pounds because of a long drawn out illness with diarrhea, vomiting, anorexia, *etc.* An exploratory ceilotomy revealed a regional ileitis, six inches in extent, two feet above the ileocecal valve, with the characteristic intestinal findings and tremendously enlarged nodes in the mesentery. The involved bowel and thickened mesentery were resected, and an end-to-end anastomosis established. She made an uneventful recovery and rapidly gained weight. She remained apparently well for about a year, when she began complaining of a loss of appetite, with occasional crampy pains in the abdomen; a palpable mass could be felt in the lower right quadrant. There had been left, I suppose, a foot and a half of ileum between the valve and the resection.

We operated upon her again and found about six inches of the terminal ileum involved, with the usual characteristic, striking change between the diseased ileum and the perfectly normal cecum. On eviscerating her pretty thoroughly, we found just below the site of the previous anastomosis a small area, perhaps two inches long, of definite thickening but without constriction, and in addition, perhaps a foot above the previous anastomosis, another area, two and a half or three inches long, with definite involvement.

With the bowel well out on the table, it could then be seen that there was a difference in the appearance of the bowel between the segments of diseased ileum, and the flat, ribbon-like, perfectly normal ileum. It was apparent that there was a difference between this normal ileum and the ileum between the actual areas of disease that could be appreciated only on comparison.

A wide resection, from the perfectly normal, flat, thin, ribbon-like ileum, well above the disease to the transverse colon and an end-to-end anastomosis were performed. I am interested to know if the bowel between the areas of frank disease was different from the normal bowel in which the second resection was performed.

DR. CHARLES G. MIXTER (Boston, Mass.): I would like to speak about one point in technic which I think might be of interest: Lately, the question has arisen, on account of the number of recurrences that have been reported, of the possibility of this particular lesion being classified again as a medical lesion instead of a surgical one.

Our experience has been that approximately 40 per cent of our cases have shown complications of fistulae, either to the large bowel, to the bladder or to the skin, or as multiple lesions. Such lesions appear definitely surgical—surgery is used in other conditions where we do not necessarily expect to cure the underlying disease, for example, peptic ulcers. If we can show that a good percentage of cases of regional enteritis which have been disabled, can be returned to health, it seems to me that the lesion should be classified as a surgical one.

Recently, I looked up our cases during the past seven years, and the two oldest cases, seven years and six years after operation, have each put on about 50 pounds in weight, and they have returned to their occupations.

I believe that possibly some of the recurrences that have been reported may have been due to inadequate removal of the mesentery. If the mesentery is the original site of the disease, as perhaps Reichert's work would lead us to believe, or if, on the other hand, the lesion starts in the small bowel and then travels to the mesenteric nodes, in either case, there is a perfectly good probability of extension taking place to adjacent bowel after resection, if those infected nodes have not been or cannot be removed.

I do not say that one can remove the complete segment of involved mesentery in all cases, but I do believe we should make the effort to make as wide a resection of the mesentery as we do of the bowel itself.

DR. JOHN HOMANS (Boston, Mass.): Doctor Kerr asked for information as to recurrences and among the six cases upon which I have operated: There has been one recurrence, which was of so striking a nature that it is worth reporting; also, in some of the other cases, the limit of the disease has been so uncertain that I can hardly believe anyone could have been sure, without sectioning specimens from a long area of bowel, that he could tell how far the disease had spread.

The recurrence was one of a typical ileitis in a man with a great many inflamed nodes in his mesentery, and a very considerable area of the mesentery was involved, so here I think that Doctor Mixter's suggestion as to the cause of the recurrence may apply.

I resected an area including perhaps a foot above the disease, removed the cecum and the ascending colon, and made an end-to-side anastomosis. The recurrence evidenced itself within two weeks. The patient was then treated medically for a year or more, after which he was again explored. So much disease was found in the mesentery and so much bowel apparently involved, that it was felt he was incurable. A half-hearted attempt was made to carry him along by establishing an anastomosis between the normal bowel and the transverse colon, which did no good.

He then went to Doctor Crohn, under whose direction he was subjected to a resection, since which operation, he has suffered another recurrence, so I fancy that he is actually incurable, perhaps for the reason that Doctor Mixter suggested—too much of his mesentery has become involved in the disease and causes reinfection of the bowel.

I should also like to add that in two cases I have seen the disease in the cecum and ascending colon. In one of these, I had resected around the corner of the transverse colon into what I thought was normal bowel, and

the pathologist reported that halfway across the transverse colon the disease was still present, so in that case nobody could have been sure.

Another recent instance occurred in a male, age 21, who had had the disease for exactly two hours, symptomatically, before I operated upon him. It was an unusual case, in which there was nothing to be noticed except a very slight thickening of the cecum and ascending colon and only slight dilatation of the lower ileum for perhaps a couple of feet. An appendicectomy was performed. Subsequent roentgenologic examinations showed only the faintest possible involvement of the cecum. The rest of the bowel appeared completely normal.

I should add that there were a few large nodes in the mesentery; I feel that there was no way of telling how much should have been resected. My own feeling is that this disease is a rather roving one, that is, not by any means confined to the small bowel, that the extent of the disease in the mesentery sometimes makes it incurable, and that it may extend so far down the large bowel that no one, even on the operating table, can be sure of its extent.

DR. CLAUDE F. DIXON (closing): Just as frequently happens, the discussion of the paper has been more interesting than the presentation itself. Doctor Kerr has mentioned an important point, namely, that in this condition, which we have called regional enteritis, there may be apparently normal portions of bowel between involved segments. Five or six such cases have been observed at the clinic. In these instances, although there is no gross evidence of pathologic change in the intestinal wall, the apparently normal segment is markedly dilated, as a rule.

The early phase of segmental enteritis may produce rather marked symptoms without gross evidence of disease on the serosal surface of the intestine. A case upon which I operated serves to emphasize this point. The roentgenologist had made a diagnosis of terminal ileitis but I was unable to detect any gross abnormality in the ileum or cecum and I closed the abdominal incision without doing anything further than to make a careful inspection. Eight months later, because of an exacerbation of the symptoms, the patient was operated upon again. The surgeon found marked thickening of the wall of the terminal eight or ten inches of the ileum, and that this portion of the intestine was covered by a dense exudate. He resected the intestine and satisfactory convalescence followed. In these early cases, the ulceration in the mucosa is apparently the defect which the roentgenologist finds. By placing a light behind the suspected segment of intestine and transilluminating it, one may be able to detect a small defect such as an ulceration or a polyp. During the past few months I have employed a cold Cameron light for this purpose and have found it most helpful.

Doctor Lehman's case is extremely interesting to me. It emphasizes that even if a portion of the diseased bowel is left in situ, recovery may follow. However, I believe that when one is dealing with true segmental enteritis, extensive recurrence of the disease is most likely to follow unless radical resection is carried out. And I agree with Doctor Mixter that a radical excision of mesentery should be made if enlarged nodes are present.

Regarding the method of anastomosis of the intestine: I realize that many surgeons employ end-to-end or end-to-side anastomoses; nevertheless, if I am to carry out the procedure I feel, as a rule, that the side-to-side method will be found the safest.

PERIANAL FISTULAE AS A COMPLICATION OF REGIONAL ILEITIS

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SINUS tracts and fistulae of various kinds constitute one of the most constant manifestations of ileitis; they originate in the distal ileum which then constitutes the proximal end of the tract. The fistulae terminate on a surface of the body, epidermal or endodermal. The most common site of termination is on the abdominal wall, the fistulous tract burrowing through the scar of a previous operation (usually an appendicectomy). Where no operative scar is present on the abdominal wall, we have rarely seen fistulae. Other common sites of termination are: Segments of the colon, particularly the cecum, the ascending colon and the ubiquitous sigmoid loop of the pelvic colon; vagina, rectum or ureters.

Of late, in addition, we have received the oral description of a case of ileitis whose earliest and first manifestation was a fecal fistula, making its exit as a perinephric abscess in the right lumbar paravertebral area (Dr. A. Snapper of Amsterdam, Holland). Another case seen by one of us (B.B.C.) presented four lumbar fistulae placed in linear arrangement vertically in the right lumbar area, accompanied by two inguinal fistulae, all of them discharging feces. In neither of these lumbar cases were intestinal symptoms noted, nor was there any suspicion of an intestinal disease until the fecal content of the fistulous abscesses became apparent.

One of the most common types of fistulae complicating ileitis, however, remains to be described; namely, the perianal fistulae. We were not at first conscious of the fact that anal and perianal fistulae constitute a frequent complication of the condition. But with more careful observation we have noted that eight out of 50 analyzed cases of regional ileitis exhibited anal fistulae as a complication, an incidence of 14 per cent. Probably this figure represents much too modest an estimate, for fistula-in-ano, unless questioned for in taking a clinical history, may easily be overlooked, and unless searched for in a complete physical examination, may be completely missed.

It is remarkable to note how frequently the fistula-in-ano was the first clinical manifestation of ileitis, even preceding consciousness of disturbed intestinal function. Such fistulae are usually local phenomena originating, presumably, in a crypt of Morgagni, infected by the contaminated ileal con-

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tents transported to this spot; the tract makes its exit either in the anal region itself, commonly between or through external hemorrhoids, at the anocutaneous margin, on one of the buttocks, in the perineum, or, in women, as a rectovaginal fistula. They may be single or multiple; they may apparently close up for a time, but almost invariably reopen and leak a thin serous, purulent or fecopurulent discharge. They persist as long as the ileitis persists and is active; they close spontaneously when the affected small intestine is resected and may heal when a short-circuiting operation is successful. The rectovaginal fistula is the most persistent and requires surgical removal by dissection, a procedure which is often not successful and frequently must be repeated.

It is of course recognized that fistula-in-ano is a common disease associated with many diarrheal conditions of various origins. On the other hand, simple fistula-in-ano most frequently is a purely local manifestation, independent of any previous or associated disease, or accompanying simple constipation; the nonspecific fistula-in-ano is the type most commonly seen. Tuberculosis, while reputedly the cause of most of these fistulous tracts, is rarely found and is actually an infrequent offender, occurring in only about 1 per cent of instances of fistula-in-ano. Nonspecific ulcerative colitis is commonly complicated by perianal fistulae, according to Bargen, being present in 26 out of 697 instances, or 3.7 per cent of cases of ulcerative colitis. Probably any diarrhea, caused by inflammatory disease of the intestine, may be and is, complicated by fistula-in-ano, no matter how distant the source of the diseased segment. Submucosal infection in the crypts of Morgagni forms a low-grade abscess which breaks inward to the rectal mucosa and outward to the buttock or perianal region.

Noninfectious diarrheas do not produce perianal fistulae. We have never seen gastrogenous, neurogenic or allergic diarrhea, no matter how severe, complicated by fistula-in-ano.

The majority of perineal fistulae complicating ileitis are of local origin in the crypts of Morgagni. We have good reason, however, to suspect that there exist instances of *direct* fistulization from ileum to rectum or to perirectal spaces and then continuously downward to the perineum. The long fistulae originating from the terminal ileum are usually not direct in their course. They are very tortuous and conduct intestinal contents to the perineum. They become secondarily infected, particularly when they head downward and approach the pelvis. Low-grade pelvic abscesses frequently form; the infection seeps or spreads downward into the perirectal or ischiorectal spaces forming a perirectal abscess to the right of the rectal wall as it traverses the pelvis in its extraperitoneal course. This abscess continues to burrow downward and inward to point into the rectal cavity or somewhere near the anus. It is difficult to prove this point as we have not been able to follow such a fistulous tract throughout its continuity. But we have been able to trace, roentgenologically, the fistulous tract from ileum to pararectal abscess; again, in particular instances, we have been able to visualize an oc-

casional peri-anal external fistula, by injecting lipiodol or sodium iodide into its tract and, by roentgenography, prove that its course carries it upward and toward the ampulla of the rectum. Appended are three rather typical case histories which illustrate the existence and course of such "long" fistulous tracts.

CASE REPORTS

Case 1.—We are indebted to Dr. Joseph Tomarkin of Cleveland, Ohio, and Dr. A. A. Berg for data on this case. Hosp. No. 399880: S. G., white, male, age 26, had been complaining of intermittent attacks of abdominal pain for one and one-half years. This pain localized in the center of the abdomen but was not associated with nausea or vomiting. Examination revealed tenderness over McBurney's point accompanied by definite spasticity of the right rectus abdominis. There was also tenderness in the right side of the pelvis on rectal examination. No masses were felt. Temperature was 100° F., leukocyte count, 16,400. Urine analysis was negative. *Preoperative Diagnosis:* Acute appendicitis.

Primary Operation.—The appendix was found to be much enlarged and appeared gangrenous. It was situated in the mesenteric fold of the ileum and presented a small pocket of pus at its tip. The surgeon noted some redness and thickening of the ileum, contiguous to the appendix and extending for a distance of two and one-half to three inches along the terminal loop of the ileum. The appendix was removed and the abdomen was closed with drainage. The patient made an uneventful recovery. *Pathologic Diagnosis:* "Chronic catarrhal and subacute appendicitis and periappendicitis."

He was readmitted to the same hospital in Cleveland, Ohio, two and one-half months later, because of the recurrence of vague epigastric and umbilical pain. There had been no nausea or vomiting and his bowels were regular. Temperature, normal. On this occasion a mass was palpable by rectum; due to this a diagnosis of regional ileitis was suggested. Roentgenologic examination, however, showed no deformities in the ileum or cecum. As a result he was treated conservatively and when, after a few days, the mass, which had been felt by rectum, diminished in size, the patient was discharged.

One month later, he developed colicky pain in the left lower quadrant. There was no nausea or vomiting, diarrhea or constipation. He was running a subfebrile course and had lost a good deal of weight. Examination per rectum revealed a large mass. This was explored with a needle inserted through the lateral rectal wall, and pus was obtained. The abscess cavity was, therefore, drained through the rectum. Biopsy of some tissue from the wall of the abscess was reported as having an acute inflammatory reaction. After some improvement, the fever and pain recurred and the abscess cavity was again drained. About two ounces of pus were obtained and he began to improve rapidly. One month later, he was again readmitted to the same institution, suffering with marked diarrhea and a total loss of 75 pounds in weight. His stools were bloody and defecation was preceded by abdominal cramps. Roentgenologic examination of the small intestine, at this time, showed a typical ileitis with internal fistula formation. He was transfused and transferred to the Mount Sinai Hospital in New York City.

Secondary Operation.—October 30, 1936: He was explored by Dr. A. A. Berg, and was subjected to an ileocecal resection with ileo-ascending colostomy and excision of fistulae between ileum and rectum. It was noted that the terminal foot of the ileum was thickened, indurated, and chronically inflamed. There were numerous peritoneal adhesions between loops of ileum. The mesentery of the affected ileum contained numerous large, oval, grayish nodes. A fistulous tract was present extending down along the right pelvic wall to the rectum about one inch above the anus.

Pathologic Examination, Gross: The resected intestine revealed chronic and acute

ulcerative terminal ileitis with multiple fistulae and subacute peritonitis. Eight centimeters from the ileocecal valve there was a perforation, about one centimeter in diameter, originating in the lumen of the ileum, and transversing the region of the mesentery. This was lined by reddish-gray granulation tissue. Four centimeters proximal to this fistula, and on the opposite side of the mesentery, there was another perforation of the bowel. The submucosa was thickened and showed numerous fistulous tracts. His postoperative course was complicated by a pneumonia which led to a lethal outcome after about two weeks.

Case 2.—Service of Dr. Richard Lewisohn. Hosp. No. 384578: H. B., male, age 21, had developed pain, redness and swelling in the perianal region two years previously. An abscess was incised, pus evacuated and the area gradually, but not completely, closed over. About 19 months later a probe was inserted into the persistent opening for a variable distance upward. The fistula refused to heal and continued to discharge thin purulent material.

About six months before admission (one and one-half years after the first appearance of the fistula-in-ano) he developed cramp-like supra-umbilical pains, nonradiating and unrelated to meals. This pain continued for five weeks with afternoon rises of temperature to 101° F. Appendicectomy was performed elsewhere and a "ruptured appendix with abscess" was found and drainage was instituted. The drain was removed in one week and the wound healed completely in 12 days. As he was about to be discharged, he developed pain in the right hip extending down to the thigh and associated with fever. The wound was reopened and again drained. A sinus to the abdominal wall formed which persisted for one month, but then closed; he was considered ready for discharge. At this time, he developed pain in the right lower quadrant where he noted a red, tender, painful, swollen area. This was incised and drained, and continued to drain up to the time he came under our observation, a period of four months. Six weeks before this period of observation the original incision reopened and remained as a draining sinus in the anterior abdominal wall. The tender mass in the right lower quadrant of the abdomen now reappeared.

Physical Examination.—The following significant features were noted: There were two incisional scars in the right lower quadrant. The medial scar was a three inch pararectus incision beginning just below the level of the umbilicus. It presented a pinhead-sized opening at its lower end. This orifice was surrounded by granulation tissue and exuded pus on pressure. The lateral incision paralleled Poupart's ligament and extended just above it two inches from the anterior superior iliac spine. It was surrounded by granulation tissue and showed a greenish, foul discharge. There was a mass just lateral to the pararectus incision over which tenderness and rigidity could be elicited.

On the left buttock, one inch from the anus and in the "4 o'clock position," was a crusted polypoid mass from which pus exuded. This was surrounded by an area of induration above which a second opening could be seen.

Injection of lipiodol into the upper abdominal sinus, with occlusion of the lower one, outlined several tortuous sinus tracts. The greater part of the lipiodol traveled downward and puddled in the pelvis.

Gastro-intestinal roentgenograms showed no evidence of a lesion of the stomach or duodenum. Observations of the small intestine, made at hourly intervals, showed the jejunal loops displaced to the left by a mass in the right iliac fossa. The terminal ileum was narrowed, irregular and markedly deformed, indicating the presence of a nonspecific ulcerating lesion involving the ileum and cecum.

Operation.—September, 1935: Dr. Leon Ginzburg. The ileum was cut across above the involved area, both ends were turned in and an ileotransverse colostomy was performed, thus excluding the mass from the fecal stream. His physical condition precluded any extensive exploration. His postoperative course was uneventful and the fistula-in-ano became asymptomatic. The discharge from the abdominal fistulae grad-

ually diminished, the fistula eventually closing. The fistula-in-ano closed spontaneously after the abdominal procedure, and has remained closed to date.

Case 3.—Service of Dr. Richard Lewisohn. Hosp. No. 407492: S. F., white, female, age 24, had been perfectly well until six and one-half years before coming under observation, when she suddenly developed diarrhea while undergoing reducing procedure. There were as many as 20 nonbloody movements daily, accompanied by severe perineal pain. Fever was absent. Six months after the onset, a "rectal cyst" was observed in another institution and incised. Four months after this operation the diarrhea subsided spontaneously. A report from the above hospital indicated that she had had a perirectal and a vulvovaginal abscess, both of which had been incised and drained.

Six months after the first operation, she developed an abscess of the right labia majora, which was incised and drained. Shortly thereafter a swelling of the right buttock developed, which was also incised and drained, as was also an abscess of the left labia. The surgeon reported these as simple ischiorectal abscesses. One and one-half years after the onset, and soon after the drainage of the second labial abscess, a rectovaginal fistula was found. This fistula was repeatedly operated upon, but never with successful issue. Feces were passed per vaginam and there was a persistent vaginal discharge. The failure of the rectovaginal fistula to close led to further investigation and it was found that there was a sinus tract in the rectovaginal septum which ran so far up that "it was necessary to leave the innermost portion of it behind because of the danger of entering the abdominal cavity." At this time a roentgenologic examination of the gastro-intestinal tract showed a stasis in the small intestine which was attributed to adhesions. Shortly thereafter, a celiotomy for "intestinal obstruction" was performed and an appendicectomy was carried out. No details of the intra-abdominal findings were given.

About ten months before coming under our observation, she was suddenly seized with severe abdominal pain and admitted to another institution. Reports from this hospital indicate that the patient apparently had had a partial intestinal obstruction, which was attributed to a "chronic adhesive peritonitis." During all the years of her illness, the patient had suffered from diffuse lower abdominal cramps which were present daily, and were accompanied by frequent recurrences of her watery diarrhea. In the five weeks preceding our observations, the cramps and diarrhea had increased to the point of necessitating hospitalization.

Physical Examination.—Mt. Sinai Hospital, New York: The patient was a well-developed and well-nourished young white female who presented a soft abdomen which was not distended or tender. There was a well healed midline hypogastric scar. No intra-abdominal masses were felt. There were several well healed scars in the perineum. Gynecologic examination showed a fistulous opening just within the vagina, about one-half inch above the fourchette, and leading into the rectum. Tuberculin tests were negative. Roentgenologic examination of the chest showed no abnormalities. Blood count showed only a mild secondary anemia. The blood Wassermann test was negative. Blood chemistry studies on admission were essentially normal. Examination of the stool showed the presence of occult blood but no ova or parasites. There were no serologic or cultural evidences of dysentery infection. Examination of gastric contents showed the presence of free acid. A gastro-intestinal series showed a dilatation of the distal jejunum and ileum, with evidence of an ulcerating lesion in the latter. Under observation, she progressively lost weight and had repeated episodes of fever and abdominal cramps.

Operation.—A typical regional ileitis, with marked enlargement of the mesenteric nodes and massive adhesions which matted together various loops of small intestine was demonstrated. A fistula was found connecting the ileum and sigmoid colon. This was divided, and the involved ileum, cecum and ascending colon resected and and ileotransverse colostomy performed. It was then found that there was a fistulous tract in the

mesentery extending down toward the pelvis. It was not explored further due to the duration of the operative procedure.

Following a prolonged postoperative convalescence, the patient was discharged much improved, but with the rectovaginal fistula still patent. It was considered wise to postpone repair of this fistula to a later time.

Discussion.—We may summarize these three cases as follows: In Case 1, a fistulous tract originated in the ileum and burrowed down into the pelvis, presenting itself as an abscess which reached to within an inch of the perineum before it was incised. The second case presented a small fecal fistula opening in the perineum. This was the result of an ischiorectal abscess which antedated the onset of the intestinal symptoms, but which eventually pointed to the presence of a regional ileitis. In addition, the patient presented two fistulae to the abdominal wall. The injection of lipiodol through the abdominal wall fistulae led to a cavity deep in the pelvis. A short-circuiting operation resulted in the spontaneous healing of all the fistulous tracts. In the third case, we were confronted with two fistulous tracts, both directed toward the pelvic floor—the one extending downward from the ileum to the ischiorectal fossa, the other extending upward from the perineum through the rectovaginal septum approaching the same area in the pararectal space.

In a recent analysis of the clinical histories of a series of 56 consecutive cases of regional ileitis, we were struck by the frequent occurrence of "fistula-in-ano" as narrated by the patient in discussing past gastro-intestinal disorders. Several of these patients presented perineal scars as evidence of previous surgical interference and in a few instances several nipple-like excrescences were found from which purulent material could be expressed. Objective data on such cases were observed in eight instances in this series, indicating an incidence of about 14 per cent.

Such perirectal or perianal suppuration would not be considered an unusual complication in a disease process so prone to manifest itself with diarrhea, were it not for its high incidence and unusual clinical features. In an analysis of 693 cases of chronic ulcerative colitis, Bargen found 26 cases of perirectal abscess and fistula-in-ano, which he considered to be due to infection of the crypts of Morgagni with subsequent invasion of the perirectal tissues and abscess formation. These figures would indicate an incidence of 3.7 per cent of fistula-in-ano or perirectal abscess in chronic ulcerative colitis. In a similar analysis of a mixed group of patients with various complaints referable to the anus, rectum or colon, he found fistula-in-ano to be present in 5 per cent of the total series.

The well-known tendency to intra-abdominal sinus and fistula formation shown by the pathologic process characteristic of regional ileitis, led us to believe that the perineal process might be another expression of the same burrowing capacity so frequently found in the production of fistulous connections between ileum and intra-abdominal viscera or abdominal wall.

These long or continuous fistulae are uncommon in comparison with the

more frequently observed simple, short fistula-in-ano. They are, however, exceedingly interesting and will bear careful clinical observation and recording. As a clinical manifestation, they frequently precede all symptoms which may cause suspicion of, or direct attention to the intestinal tract and particularly, the ileum.

For that matter, all fistulae which occur in association with ileitis may precede the consciousness of an intestinal disturbance. This applies to the fistulae in the abdominal wall which follow a futile exploratory operation, as well as to fistulae to segments of the colon, to the inguinal or lumbar regions, on fistula-in-ano. The original disease is of so subdued a nature and runs such a mild chronic course that the fistulae often precede the history or consciousness of diarrheal disturbances. In fact, of late we have seen ileitis with only constipation, but with fistulae-in-ano already recognizable.

Every case which presents itself with fistula-in-ano should deserve careful clinical preoperative study. The general conception that most fistulae-in-ano are tuberculous in origin is entirely erroneous; according to the pathologic records of the Mt. Sinai Hospital (Dr. Paul Klemperer), less than 1 per cent of granulation tissue removed at operation and subjected to study, reveals the tuberculous nature of such fistulous tracts.

Every case of fistula-in-ano is entitled to a proctoscopy, to rule out ulcerative colitis; to a careful roentgenologic study of the intestinal tract; to a roentgenogram of the chest to establish the existence or nonexistence of tuberculosis; and to a careful history and an even more careful physical examination.

In any case suspected of ileitis in which the roentgenologic findings are inconclusive and not convincing, the existence of one or more perianal fistulous tracts should materially support the diagnosis of an ileitis, providing of course that ulcerative proctitis or colitis is excluded.

Treatment.—Perianal fistulae, pararectal abscesses and rectovaginal fistulae originating from ileitis are best handled surgically by efforts directed to remove the primary disease. When the ileitis is entirely resected, the fistulae almost invariably close and heal permanently. Our experience with short-circuiting operations is insufficient, but we have reason to doubt that they will uniformly, or even in a majority of the cases, lead to healing of the fistulous tracts in the anal region; occasionally, however, such short-circuiting operations are successful in causing healing of the fistulae.

Persistent diarrhea is a deterrent to healing of such tracts; it is better to resect the ileitis in its continuity rather than leave a persistent focus of infection within the intestinal lumen with its recognized capabilities as a trouble-maker.

Where the fistulae fail to heal spontaneously after the ileitis has been properly handled, local excision of the tract, curettage and suture should be instituted, provided the bowel function has been restored to normal. In our experience the rectovaginal fistulae always require operation and cauterization, usually, unfortunately, with little success, so that many attempts are required before a satisfactory result can be obtained.

ACUTE CHOLECYSTITIS

THE RESULTS OF OPERATION WITHIN FORTY-EIGHT HOURS OF THE ONSET OF SYMPTOMS

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THERE has been a steadily increasing interest in early operation for acute cholecystitis during the past decade, but the term "early operation" seems to mean anything from early in the disease to soon after admission to the hospital, although the patient may have been previously ill at home for some days. To evaluate results, it is desirable to set a definite time and, for the purpose of this study, we have chosen the first 48 hours from the *onset* of the symptoms of the acute attack.

TABLE I

OPERATIONS FOR ACUTE CHOLECYSTITIS WITHIN 48 HOURS OF THE ONSET

Surgeon	Number	Cholecystectomy	Cholecystostomy	Deaths
Graham[1]	20	18	2	1
Heuer[2]	50	49	1	2
Stone[3]	2	2	0	0
Walters[4]	7	6	1	0
Taylor[5]	19	?	?	1
Graham and Hoefle	51	51	0	2
Kunath[6]	6	0	6	0
Zinninger[7]	12	?	?	0
Totals	167	126	10	6
Mortality Percentage				3.59%

Table I shows that in 167 cases which were operated upon within 48 hours of the onset, there occurred six deaths, a mortality rate of 3.59 per cent. We are more concerned with the *promptness* of the operation than with the *type* of procedure, but cholecystectomy was the operation of choice in these cases, while cholecystostomy was reserved for the more critical cases.

There are certain factors that make a cholecystectomy for acute cholecystitis more difficult than one performed in the quiescent period. The gallbladder is often tense and distended. The tissues are more friable and the bleeding is more profuse. There is more swelling around the cystic duct. It may be necessary to aspirate the gallbladder, and we usually prefer in these acute cases to remove it from above downward, controlling the bleeding from the liver bed by the pressure of a gauze pad and a retractor. The cystic duct is carefully ligated, using traction toward the common duct instead of away from it. This prevents the possibility of pulling the cystic duct off accidentally at a lower level than was intended. If, for any reason, the cystic artery escapes and bleeds, it is easy to control this and secure a

dry field by the use of a small angular retractor or the finger in the foramen of Winslow making pressure on the hepatic artery until the bleeding vessel has been clamped and ligated. An oozing liver bed, that cannot be obliterated, can be quickly peritonealized and rendered dry by a free omental graft lightly tacked in place by a few interrupted sutures. A large percentage of cultures taken during the first 48 hours remain sterile and, therefore, infection is not a major problem at this time.

It has frequently been said that acute cholecystitis is not like acute appendicitis, and that there is not the same necessity for prompt operative interference. The statistics in Table II show the mortality at various periods after the onset of symptoms.

TABLE II

ONE HUNDRED CONSECUTIVE CHOLECYSTECTOMIES FOR ACUTE CHOLECYSTITIS

From the First Surgical Service of the Methodist Hospital, Brooklyn, N. Y.
January 1, 1929, to October 1, 1937

Onset of Symptoms to Operation	Edematous		Suppurative		Gangrenous		Perforated	
	No.	Died	No.	Died	No.	Died	No.	Died
Up to 48 hours*	26	0	19	0	3	0	3	2
2 to 5 days†	14	1	8	1	5	0	0	0
5 days or more‡	14	1	3	1	4	2	1	1
Total	54	2	30	2	12	2	4	3

* Acute cholecystitis operated upon within 48 hours—51 cases—2 deaths—3.92 per cent.
† Acute cholecystitis operated upon 2 to 5 days—27 cases—2 deaths—7.40 per cent.
‡ Acute cholecystitis operated upon 5 days or more—22 cases—5 deaths—22.72 per cent.
Total mortality in 100 cases—9 deaths—9.0 per cent.

A delay of more than five days gives a high operative mortality, and raises the question of whether operation should be performed or delay advised. This must be decided for each individual case. When operation is performed in these cases, the further question of what operation is indicated will arise. Note that there were three patients with gangrenous gallbladders, and there were also three patients with perforated gallbladders, within 48 hours of the onset of the attack; and two of the latter died. Harvey Stone[3] cites an instance of a totally gangrenous gallbladder, with autolysis, which he found at operation, seven hours after the first severe pain which marked the onset. Gangrene was also present in another case. In a third patient, who was being studied for obscure digestive symptoms of three months' duration, a perforation of the gallbladder with resultant peritonitis suddenly occurred, necessitating an emergency operation. In Kunath's[6] six cases, there was one patient with a gallbladder already gangrenous, and two cases in which perforation had occurred. In Taylor's[5] 19 cases, operated upon within 48 hours, five were already gangrenous. These are not rare or unusual events. Most of the recently published series of cases of acute cholecystitis show an incidence of gangrene of about 20 per cent.

In the last analysis, the greatest emphasis must be placed upon the mor-

tality statistics. Whatever method will save the most lives should be employed. In Pennoyer's[8] series of 300 cases of acute cholecystitis, treated in the Roosevelt Hospital, where the general policy was to delay whenever possible, the mortality was 10 per cent. This presents a striking contrast to the 3.59 per cent mortality in the cases operated upon within 48 hours of the onset, and is a strong argument in favor of a determined effort to obtain these cases for operation within 48 hours. Consideration must also be given to the other disadvantages of delay; namely, the days of pain, the sleepless nights, the starvation and debility, the long hospitalization and increased expense.

It is difficult to see two sides to this question, when it is so evident that a lowering in mortality could be accomplished so easily by education of the laity and cooperation between the family physician and the surgeon to secure a prompt operation, early in the attack, for every person suffering from acute cholecystitis who is a proper operative risk.

SUMMARY

(1) A series of 167 cases of acute cholecystitis operated upon within 48 hours of the onset of the attack has been collected. The mortality was 3.59 per cent.

(2) The difficulties of operation in the acute stage have been discussed, and also the methods that can be employed to minimize these dangers.

(3) An earnest plea is made for education and effort to secure operation in acute cholecystitis within the first day or two of an attack.

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EPIDERMOID CYSTS OF THE SPLEEN

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EPIDERMOID cysts of the spleen are apparently very rare. In a fairly careful search of the literature we have been unable to find any cases of this condition reported since 1933, when Shawan[1] collected three cases and added one of his own. Custer,[2] in 1937, stated that he had seen five cases of simple epidermoid cysts of the spleen in 5,000 autopsies, but no description of them has been found in the literature. Shawan cites Libarsch as having recalled a case but no report was made. The great rarity of this pathologic condition probably accounts for the fact that epidermoid cysts are not mentioned in most surgical text-books and are omitted from some classifications of cysts of the spleen.

We were entirely unfamiliar with this peculiar tumor formation until our attention was attracted to it by the appended case:

Case 1.—Female, age 7, had been in good health until February, 1937, when she developed an upper respiratory infection. The family physician in his routine examination discovered a tumor in the upper left quadrant of the abdomen which he thought was associated with the spleen. He prescribed roentgenotherapy, but as the tumor remained unchanged after eight weeks' treatment the child was sent to the Children's Memorial Hospital. At the time of her admission, June 21, 1937, the child had no complaints and appeared to be in good health. Her past history was essentially negative.

Physical Examination disclosed nothing abnormal except a mass in the left upper quadrant of the abdomen in the region of the spleen. The tumor appeared to be freely movable and extended at least two inches below the costal border and more mesial than the usual splenic border. It extended upward nearly to the nipple, making the lower edge of the thorax bulge slightly on that side, and during inspiration the mass could be seen moving downward in the abdomen. As the tumor emerged from under the costal margin a sharp line running parallel to the costal border was palpable and the fingers sank in above the mass. Pulse, respiration and temperature were normal, as well as her blood count and uranalysis. The Wassermann test was negative but the Mantoux skin test was strongly positive.

A fluoroscopic examination of the colon showed that the splenic flexure was depressed downward with a constant position beneath the mass but with no evidence of adhesions or obstruction. A diagnosis of a splenic tumor, due to either tuberculosis or a neoplasm, was made.

Operation.—Under ether anesthesia, the abdomen was opened through an upper left rectus incision. A large cystic mass, intimately attached to the spleen, presented immediately. The cyst was tapped and 520 cc. of chocolate-colored, turbid fluid aspirated. Removal of the spleen with the cyst was then easily accomplished.

Pathologic Examination.—Gross: The specimen is an almost globular, cystic mass,

with a rim of splenic tissue at its equator. Its longest diameter is 15 cm.; its widest 12 cm. The splenic tissue at the hilus is replaced by a cystic dome (Fig. 1*a*), measuring 12x8x3.8 cm. There is a patch of gray-white tissue (Fig. 1*b*), moderately firm in consistency, 4.5x3.0x0.4 cm., slightly lateral to the peak of this dome. There is a similar

FIG. 1

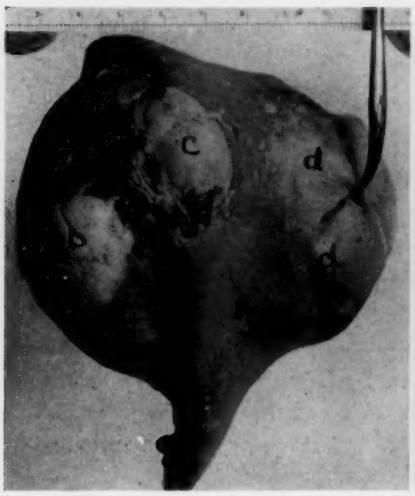

FIG. 2

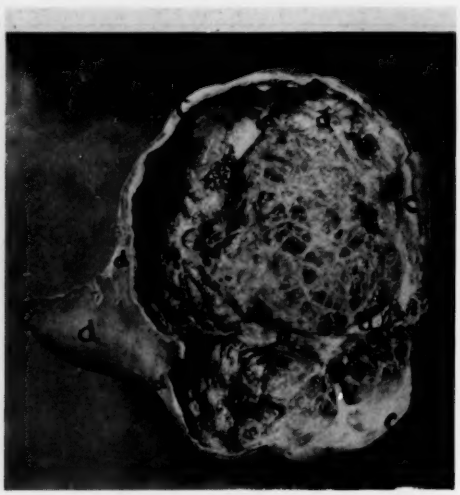

FIG. 1.—Exterior of the specimen. (a) Cystic dome at hilus region. (b) Fibrous patch. (c) Fibrous patch. (d) Costal portions of cyst. (e) Triangular projections of splenic tissue.
FIG. 2.—Internal surface of the specimen. (a) Irregularly disposed trabeculae. (b) Crypts bounded by the trabeculae. (c) Cyst capsule. (d) Surfaces made by cutting the splenic tissue.

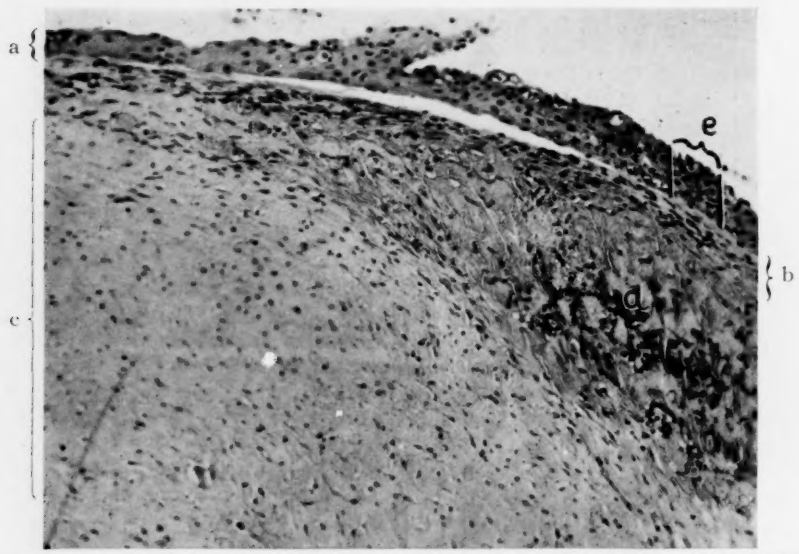

FIG. 3.—Inner wall of the cyst. (H. & E. ×100). (a) Stratified epithelium. (b) Subepithelial fibrous layer. (c) Collagenous cyst capsule. (d) Hemorrhagic area within the collagenous tissue. (e) Low power view of Fig. 4.

patch (Fig. 1*c*) 2x2.5 cm. at the junction of the hilus to the body of the spleen. The costal portion (Fig. 1*d*) of the specimen is cystic, bulging and covered by a thin, gray-white tissue, measuring 7.5x4.5x0.05 to 0.1 cm.

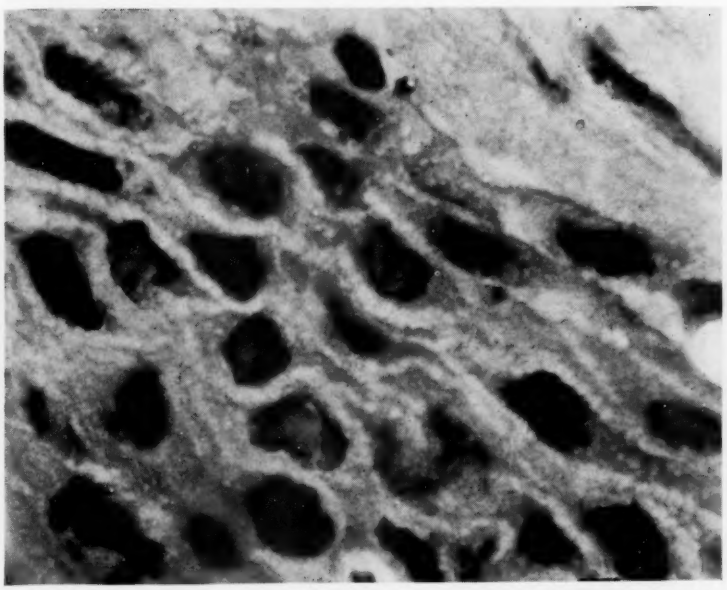

FIG. 4.—Epithelium of the cyst (H. & E. ×1100) at Fig. 3e. (a) Epithelial cell with surrounding canaliculi and intercellular bridges.

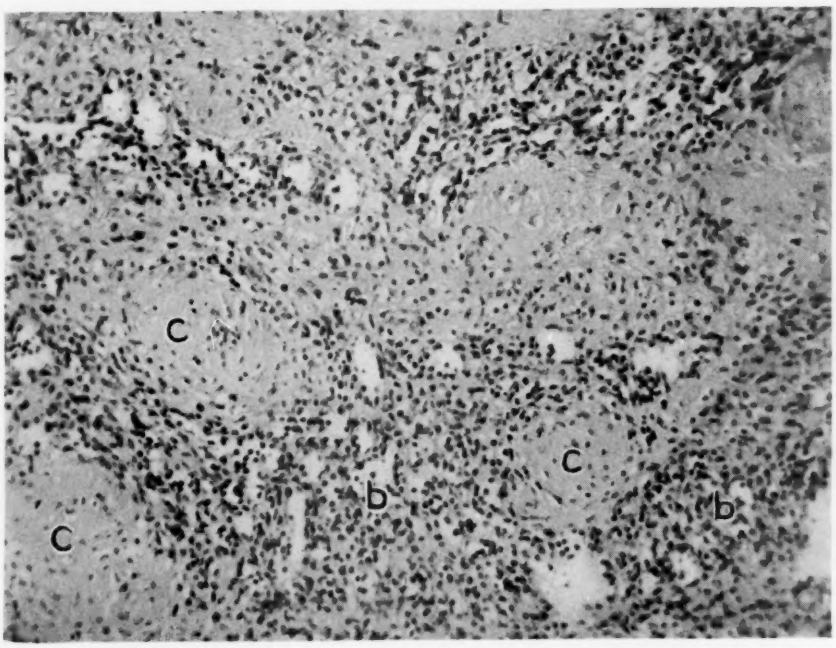

FIG. 5.—Boundary of cyst capsule and splenic tissue. (V. H. & E. ×100). (a) Innermost portion of collagenous cyst capsule. (b) Sparse splenic elements. (c) Heavy fibrous trabeculae replacing the parenchyma.

Internally there is but one large cyst present, its content 520 cc. of sterile, chocolate-colored fluid somewhat thicker than blood serum in consistency. The internal surface of the cyst contains a large number of irregularly disposed trabeculae (Fig. 2*a*) measuring from less than 1 to 8 Mm. in thickness, bounding shallow crypts (Fig. 2*b*). The trabeculae are gray-white to brown-gray. Upon this internal surface there is plastered an adherent, waxy, brown deposit. The cyst capsule (Fig. 2*c*) is made up principally of gray-white fibrous tissue 2 to 4 Mm. in thickness, except at the costal portion previously mentioned.

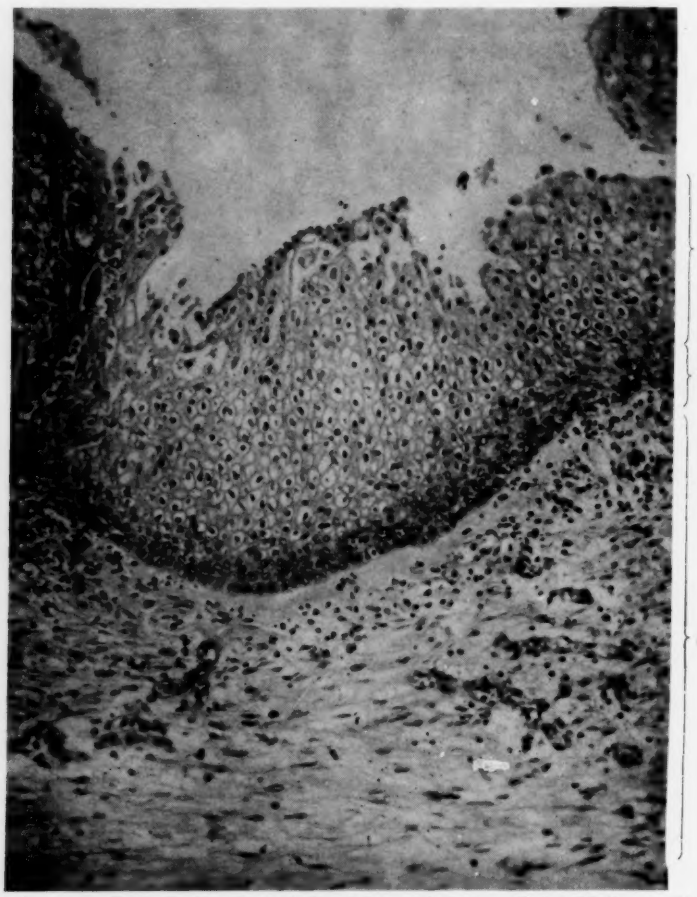

FIG. 6.—(H. & E. ×100). (a) Basal layer of the stratified epithelium. (b) Stratified epithelium beyond the basal layer. (c) Fibrous tissue with an infiltration of plasma cells, monocytes, as well as red blood cells.

The cyst completely displaces all the splenic tissue except that bordering on the hilus region, where a rim of this tissue persists, the largest area a triangular projection (Fig. 1*e*) 4x3x2.3 cm. The remainder of the splenic tissue forms a thin layer over the central portion of the cyst capsule, diminishing in thickness peripherally, almost in proportion to the distance from the hilus.

Surfaces made by cutting the splenic tissue are bluish-purple (Fig. 2*d*); the markings are not unusual except for an increase in gray-white fibrous elements adjacent to the cyst capsule.

Histology.—The cyst epithelium, where present, varies from one to nine cells in thickness, is stratified, with no keratinized cells on the surface. In the thinnest portions there is present a single or double row of flattened cells. The nuclei of the cells in the stratified epithelium are basophilic, irregularly round, oval to flat with a tendency of the long surfaces of the nuclei to lie parallel to the epithelial surface. The cytoplasm is palely basophilic and consists of irregular platelets separated from each other by an intercommunicating network of slender canaliculi. Throughout the lumina of the canaliculi there are fine linear "bridges" in nearly parallel rows, roughly perpendicular to the walls of the canaliculi (Fig. 4).

Figure 6 shows underlying the epithelium a layer of fibrous tissue, two to five cells thick, closely packed, the cells parallel to the epithelial surface. Separating the epithelium and underlying fibrous tissue layer from the splenic tissue is a thick layer of irregular trabeculae of the underlying spleen. There are small hemorrhages in each layer described, recent in nature (Fig. 3*d*).

The splenic tissue is not altered except for fibrous replacement of the parenchyma in almost a direct proportion to the contiguity with the collagenous tissue (Fig. 5).

Large areas of the cyst, as that of the costal portion, consist of nothing but fibrous tissue, no epithelial or splenic elements being present. No hair follicles, sweat glands, pigment layer or other skin appendages are present.

In the gummy, brown deposit adherent to the epithelium there are present many macrophage cells with much vacuolization. There is also present a relatively small number of red blood cells.

Studies of the fluid removed from the cyst:

Bacteriology.—Direct smear showed cell débris but no organisms.

There was no growth on various culture medias.

Chemistry.—N.P.N.—28.6 mg.

Total protein.—5.4.

Cholesterol.—Sludge, 1st spec.—620 mg., 2nd spec.—730 mg.; fluid, 1st spec.—168 mg., 2nd spec.—178 mg.

Our attention was further drawn to the subject by a case which was studied by Dr. H. Gideon Wells, pathologist at the University of Chicago, and which we are permitted to report through the courtesy of the attending surgeon, Dr. W. L. Jeffries.

Case 2.—Male. age 6 months, was born of apparently normal parents August 28, 1935. Both parents showed a negative Kahn test. On February 22, 1936, he was brought to the hospital because of fever and fretfulness. He had had recurrent attacks of vomiting and abdominal distress for a week previous to admission.

Physical Examination was negative except for the presence of a large round mass in the left hypochondrium and lumbar regions. A fluoroscopic examination of the gastrointestinal tract showed that the stomach and intestines were displaced to the right by a tumor the size of a grapefruit, which occupied the left hypochondrium. Roentgenologic examination of the urinary tract, after the injection of diodrast, showed a very tortuous, dilated left ureter and a marked dilatation of the left kidney pelvis with a large shadow in the left upper quadrant suggestive of a hydronephrosis. An examination of the blood showed nothing abnormal. A diagnosis of hydronephrosis was made.

Operation.—February 24, 1937: Under ether anesthesia, what was thought to be the left kidney was drained through a retroperitoneal approach. A quantity of clear, watery fluid with an acid reaction was removed. Unfortunately the fluid was not analyzed further. The child was discharged with a draining sinus March 4, 1936.

About six weeks later the patient was readmitted, because the sinus continued to drain, and on April 17, 1936, the left kidney and spleen were removed. The child expired the following day.

Pathologic Examination.—Gross: Figure 7 shows the fixed specimen which weighed 23 gm. (19 gm. normal for seven and one-half months). The capsule is smooth except for a small area at the lower pole where it is lacking. There is present an intrasplenic cystic cavity 4x2x1 cm. centering about the hilus. Internally, there are present trabeculae similar to those seen in Case 1, except that they are brown-gray, fewer and broader, and the crypts fewer, deeper and broader. The cyst is surrounded by a heavy fibrous capsule 2 to 3 Mm. thick, containing focal areas of calcification, and is covered throughout by splenic tissue except at the hilus. The impression gained by examination of the spleen was that originally there was present an extrasplenic cyst attached to the intrasplenic portion. No further description is given.

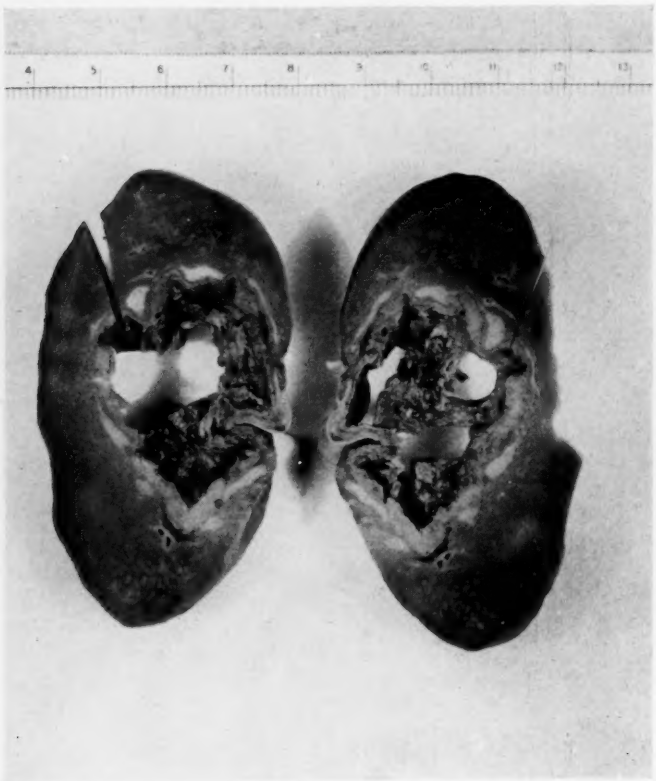

FIG. 7.—Case 2: Cut surfaces of the spleen showing interior of epidermoid cyst.

The cyst fluid, described at the first operation, was clear, watery and acid in reaction.

Histology.—The cyst epithelium is stratified. There is present a basal layer of dark staining cells two to five rows in thickness. These cells contain oval, basophilic, vesicular nuclei with the longest surfaces perpendicular of the epithelial surface. The cytoplasm is palely basophilic and consists of irregular platelets separated from one another by canaliculi and "bridges" similar to those present in Case 1. The epithelium beyond the basal layer contains as many as 20 or more cells in various stages of degeneration with fragmented and pyknotic nuclei and with cytoplasm made up of little else than a palely eosinophilic cellular membrane. This epithelium has thus the appearance of a fine eosinophilic network with pyknotic nuclei in the apertures of the net. There are no keratinized cells present.

Underlying the basal layer of the epithelium there is present a thick layer of fibrous

tissue, in some areas moderately loose, in others moderately compact. Within this layer is present an infiltration of monocytes. This fibrous tissue is continuous with the fibrous trabeculae of the spleen. Many small, scattered hemorrhages are present in the fibrous layer.

The splenic tissue is not altered except for fibrous replacement of the parenchyma adjacent to the fibrous layer. No hair follicles, sweat glands, pigment layer or other skin appendages are present.

DISCUSSION.—Epidermoid cysts of the spleen are usually large, solitary, and lined with stratified pavement epithelium with prominent intercellular bridges. No other epidermal or dermal elements have been found in the cases reported, but Custer has stated that some have been described in which the cavity was filled with sebaceous material and hair. These cysts have been reported to have weighed as much as 3 Kg. and to have contained up to 1,500 cc. of watery, chocolate colored fluid usually containing cholesterol.

The general structure of these cysts is strikingly similar from the trabeculated inner surface to the fibrous capsule and secondarily compressed spleen. The splenic tissue is usually unaltered except for gross compression and fibrous replacement adjacent to the cyst capsule.

All clinical symptoms associated with these tumors may be explained on the basis of compression of the surrounding viscera or abdominal distress from the dragging weight of the splenic mass.

Because the clinical picture is not distinctive the diagnosis is usually obscure. Pressure on the left kidney and ureter may produce confusing roentgenographic findings suggestive of urinary tract obstruction as in Case 2.

Roentgenologic examination of the gastro-intestinal tract will usually demonstrate a downward displacement of the splenic flexure of the colon. Attention was called to this finding by Ostra and Makaree. This was present in Case 1 but it is merely considered indicative of a splenic tumor. In all probability epidermoid cysts, because of their rarity and nondistinctive clinical findings, will be diagnosed only after a histologic examination.

The treatment employed in all cases has been splenectomy. When the abdomen is open, aspiration of the fluid content of the cyst, as suggested by Shawan and employed by us in Case 1, greatly facilitates the removal of the spleen with the attached cyst. However, it is very necessary to be sure that the cyst is not parasitic before employing this procedure because of the danger of peritoneal contamination.

No satisfactory explanation of the origin of epidermoid cysts of the spleen has been offered. A problem arises with the assumption that epidermoid epithelium is necessarily ectodermal in origin, and from such an assumption the necessity of accounting for ectoderm in an organ presumably arising from the mesenchyme.

An origin by *ectodermal metaplasia* similar to that of dermoid cysts has been suggested by Pohle.[3] This idea is supported by Custer's discussion, as well.

Santy, quoted by Shawan, suggests the possibility of *displacement of the wolffian body*, as does Dinand.[4] The wolffian body may produce transitional

epithelium which under certain circumstances, such as a vitamin A deficiency, may become stratified and squamous.

Shawan discusses *autochtonous formation*, according to which theory the mesoderm is capable of producing the products of any of the other primary germinal layers, including stratified squamous epithelium.

Schneider[5] was of the opinion that during splenic development some of the coelomic cavity content capable of forming epidermis was enclosed in the spleen. According to the studies of Thiel and Downey,[6] the coelomic mesothelium definitely contributes to the development of the mammalian spleen.

SUMMARY.—Herein are reported two instances of epidermoid cyst of the spleen, occuring in a girl, age 7, and a boy, age 6 months. All the patients previously reported were in the second decade of life. Case 1 meets in every respect the criteria of diagnosis. Case 2 has a few questionable features: namely, that the removal of the spleen took place two months after drainage with epithelialization from without as a possible result; that there is evidence of infection of the wall of the cyst with its possible effect on epithelial type; and that the fluid removed surgically was found to be clear rather than chocolate colored. However, Case 1 probably represents a true example of an epidermoid cyst of the spleen.

This paper is presented as a contribution to the very limited knowledge of this rather rare and interesting pathologic condition, with the hope that it may stimulate the report of additional cases and thus perhaps verify Custer's idea that epidermoid cysts of the spleen are possibly not as rare as has been supposed.

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EMBRYOMA OF THE KIDNEY (WILMS' TUMOR)

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EMBRYOMA of the kidney is one of the most malignant growths of early life and it has a very high mortality. Some divergence of opinion has developed in recent years as to the most desirable plan of treatment for this condition. In many clinics preoperative irradiation, nephrectomy, and postoperative roentgenotherapy are employed as the therapeutic plan of choice. In others, nephectomy is advocated as soon as the diagnosis is made. Some surgeons advocate a posterolumbar incision, while others see the advantage of a transperitoneal approach.

The present communication attempts to evaluate the facts available from a partial review of the literature, and in addition the study of 58 cases occurring in the Surgical Service of the Children's Hospital of Boston. Some of these cases were previously reported, in 1932, by my former associate, Dr. Charles G. Mixter.[1] Of these 58 cases, 13 have been discarded for one of two reasons—either the patient was lost track of after operation or a pathologic specimen was not obtained by operation or autopsy. Of the remaining 45 patients, 44 were operated upon and one died without operation, but a postmortem examination was made. Therefore, in every instance a pathologic as well as a clinical diagnosis is at hand, and in every case the result of the treatment is known.

It is unnecessary to review the theories of pathogenesis, as that has been ably done by others, and the facts still remain a matter of surmise. It is imperative, however, to define these tumors from a pathologic and microscopic point of view, as the nomenclature is still confused, even in recent articles. Dr. Sidney Farber has kindly contributed these data.

Pathology.—The embryoma of the kidney is a large, solid, grayish-white, encapsulated, malignant tumor probably of congenital origin. It is surrounded by a dense connective tissue capsule which is continuous with that of the kidney. The kidney usually merges gradually with the convexity of the tumor, and is separated from it by a layer of connective tissue of microscopic to gross proportions. In general, the tumor cannot be freed from the kidney. Nodules are sometimes found within the substances of the remainder of the kidney. When rapid growth occurs, hemorrhage and softening in parts of the tumor are found.

Sometimes definite, scattered cysts may be encountered. The capsule is usually tense and occasionally the tumor bulges in irregular masses at one or more places on the external surface. The pelvis of the kidney may be com-

pressed, normal, or, rarely, dilated. Pressure atrophy is usually present in the remainder of the kidney.

On miscroscopic examination the tumor presents a varied appearance. All stages from undifferentiated to partially differentiated cells of epithelial origin and of the connective tissue series (smooth muscle, striated muscle,

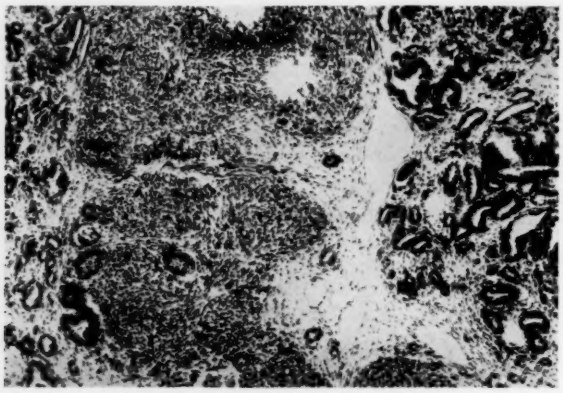

FIG. 1.—Photomicrograph of section of embryoma of kidney (S-37-483). Note tubular arrangement of epithelial cells. The midportion consists of tumor cells of the fibroblastic series. (Hematoxylin and eosin; ×100.)

sometimes bone and cartilage) may be found in the same tumor (Figs. 1 and 2). In some instances one type of cell may predominate. It is not possible to predict, with accuracy, the nature of the type of cell from the gross appearance of the tumor. Various degrees of activity are demonstrable in the same

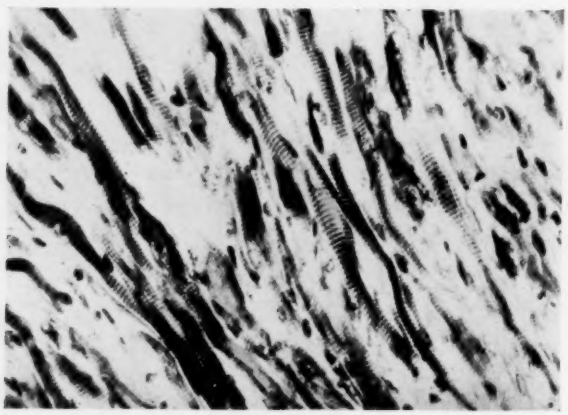

FIG. 2.—Photomicrograph of section of embryoma of kidney (S-37-483). This portion of the tumor consists entirely of striated muscle fibers. (Phosphotungstic acid hematin stain; ×500.)

tumor. Extension into small branches of the renal vein or into the renal vein itself, or invasion of the pelvis of the kidney may be encountered. The tumor is characterized by: (1) Variegated histology; (2) rapid growth after a period of slower activity; (3) the common occurrence of hemorrhage and necrosis

which may lead to rupture of the capsule; (4) the possibility of invasion of the renal vein or the pelvis of the kidney; (5) a tendency to reach a large size before metastases occur; (6) the frequency of local recurrence and metastasis to the regional lymph nodes or remote metastasis through the blood stream to the lungs.

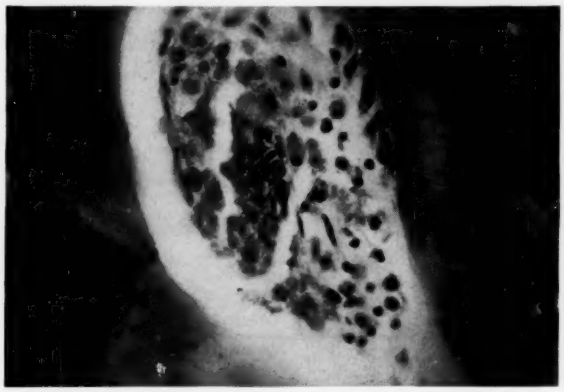

FIG. 3.—Photomicrograph of section of embryoma of kidney (S-38-40). Note well developed bone marrow surrounded by dense bone, found in one portion of the section. (Hematoxylin and eosin; ×500.)

It should be emphasized that these solid tumors of the kidney in childhood should be grouped under the term embryoma of the kidney (mixed tumor of the kidney, Wilms' tumor) despite the varied gross and histologic features which may be encountered. All tumors of this type are highly malignant.

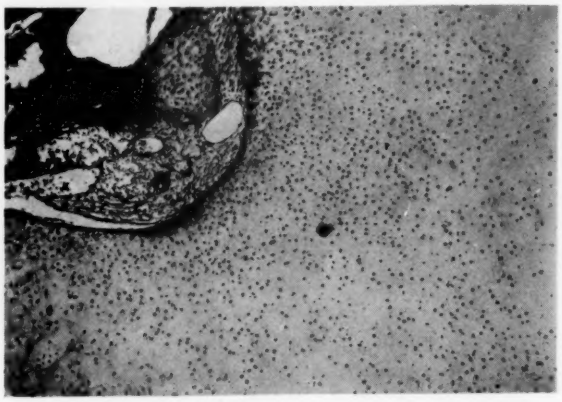

FIG. 4.—Photomicrograph of section of embryoma of kidney (S-37-483). Note well developed cartilage. In upper left hand corner is an area of loose connective tissue surrounding small islands of cartilage. The remainder of the tumor in this section consists of striated muscle and epithelial elements. (Aniline blue stain; ×100.)

The finer classification of the tumors in this group according to histologic structure is for the present, at least, of interest only to the pathologist, but has no important bearing on the prognosis or the treatment. Of real im-

portance in the pathologic examination of surgically removed embryomata of the kidney are factors, such as degree and extent of hemorrhage and necrosis, rupture of the capsule, invasion by the tumor of the renal veins or the pelvis of the kidney, and extension of the tumor through the capsule.

In infancy and childhood embryomata of the kidney must be differentiated from several other solid tumors which occur in the kidney region. The sympathetic neuroblastoma, which arises from the medulla of the adrenal gland or from medullary tissue in the immediate vicinity of the adrenal gland, is usually reddish-purple in color, well encapsulated, and is often firm and nodular in consistency. The kidney below the tumor is usually intact, although true invasion of the kidney may be found. Metastasis to the skeleton, liver or orbit takes place usually before the neuroblastoma reaches the size of the average embryoma of the kidney. The neuroblastoma on microscopic examination may contain cells of the sympathetic series in various stages of development (sympathogonia, sympathoblasts, or neuroblasts). In well fixed, suitable material the cells of the neuroblastoma are large, cylindrical and pyriform, and are often arranged in pseudorosette formation around a central zone, containing delicate fibrils representative of axis cylinder processes. Hemorrhage, often massive in type, and necrosis are common findings. Direct extension to neighboring viscera may take place before distant metastasis occurs.

The hypernephroma of the kidney, or the Grawitz tumor, is a solid tumor which arises within the kidney. We have not encountered a single example of hypernephroma in the last 20 years at the Children's Hospital. From a study of the literature, it appears likely that a true hypernephroma is of very rare occurrence in infancy and childhood, and that the term hypernephroma has been used loosely to designate an embryoma of the kidney in many instances. It is important to differentiate sharply between these two totally different tumors of the kidney. The hypernephroma is usually yellow in color in contrast to the grayish-white appearance of the embryoma of the kidney. The microscopic appearance is highly characteristic. The cells are large and have a clear to foamy cytoplasm. They grow at times in alveolar or tubular arrangement or in cords or nests of cells arranged in a fashion resembling somewhat the structure of the adrenal cortex.

Another tumor in the kidney region is the massive "unattached" retroperitoneal embryoma of renal anlage origin. This may be found on either the right or left side, or may grow nearer the midline. The tumor on gross and microscopic examination resembles closely the embryoma of the kidney. It is not attached to the kidney.

Diagnosis.—The age incidence of embryoma of the kidney is of considerable help in arriving at a diagnosis of this condition. In our series the average age was two years and three months, which corresponds moderately closely to other series found in the literature. Our youngest patient was two months and the oldest child was seven years old.

In this group there were 26 females and 19 males, while in other series a slight predominance was found among the males.

The occurrence of the tumor was equally divided between the two sides: 22 occurred in the left kidney and 22 occurred in the right kidney, while in one patient the growth was bilateral.

Therefore, it is apparent that statistics are of little diagnostic value except to show that this type of tumor is common in the first three years of life when other kidney tumors are rare, while in later life the reverse is the rule.

The diagnosis of renal embryoma is not usually very difficult. The main factors in arriving at the correct diagnosis are the clinical history and the palpation of the abdomen. Embryonal kidney tumors seldom give symptoms other than those of enlargement of the abdomen, and sometimes symptoms from pressure on the adjacent organs. The parent brings the child to the hospital, or to the physician, because she has noticed the child's abdomen increasing in size. Unfortunately, it is very common for these infants to remain in an apparently excellent state of general health and without complaints, even after the tumor has assumed enormous proportions. The child's apparent good health often results in delay before medical advice is sought. This delay adds to the high mortality.

On abdominal palpation these tumors feel solid, are not tender or fluctuant, and their location in the kidney region can be determined by bimanual examination—one hand in the costovertebral angle and the other on the front of the abdomen. The anterior hand may often outline the tumor as extending to the midline or beyond and well down into the iliac fossa. Occasionally, the tumor feels nodular but more often it is smooth and rounded. It is usually not mobile.

The urinary findings are seldom helpful in making a diagnosis. Occasionally, one finds a few red or white cells, but more often the urine examination is negative and the N.P.N. is within normal limits.

Pyelograms, either intravenous or retrograde, may be suggestive but cannot be considered conclusive evidence of the presence or absence of embryoma of the kidney. A distorted pelvis may be present in other conditions and an absolutely normal appearing pyelogram may exist in the presence of a very large embryoma (Fig. 10A and B; and Fig. 9). Though it has been our practice to obtain an intravenous or retrograde pyelogram in all cases where the diagnosis is in doubt, there are certain valid objections to making the latter a routine practice.

In the age group in which this tumor occurs, the cystoscopic examination requires a general anesthetic, which means a delay before the nephrectomy. Furthermore, it is only in the exceptional instance that the separate urine from each kidney has diagnostic significance. The one strong argument in favor of routine cystoscopic examination is the desirability of knowing the renal function of the unaffected kidney.

Aspiration biopsy, as recommended by some writers, has proved unreliable in our hands as a diagnostic method, unsafe as a surgical procedure, and is

quite likely to cause implantation recurrence. We abandoned the procedure almost 20 years ago. It seems, at least, theoretically important that as little trauma should be occasioned in handling these patients as is consistent with making a probable diagnosis. We know that the malignant cells may be cast off into the blood stream at any time and feel even slight trauma may facili-

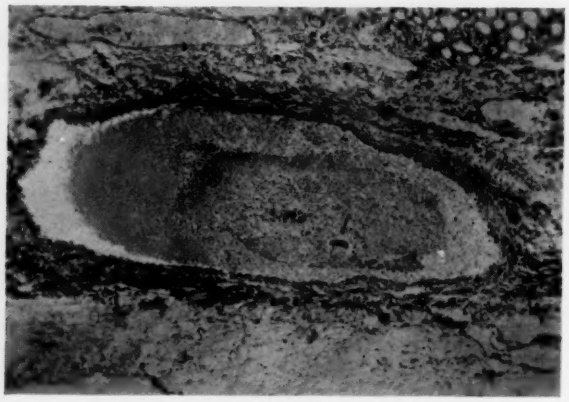

FIG. 5(A).—Photomicrograph of a section of kidney, the seat of an embryoma (S-36-370). Note the small cluster of tumor cells in branch of renal vein (arrow). Note compressed renal tissue above the vein. (Hematoxylin and eosin; ×130.)

tate this incident (Fig. 5A and B). Our convictions are strong enough along this line to not allow these patients to be examined by a multitude of students or in fact by any more people than is absolutely necessary.

Although numerous pathologic conditions might have to be differentiated

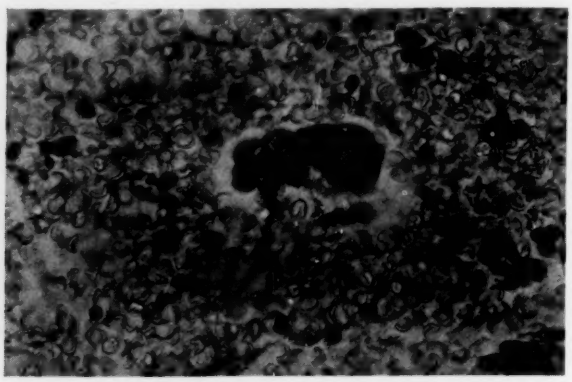

FIG. 5(B).—Photomicrograph of portion of field shown in (A) (arrow). Note cluster of tumor cells surrounded by erythrocytes in renal vein. (Hematoxylin and eosin; ×900.)

from embryoma in the diagnosis, there are only two which have caused us much concern in the age group in which this disease occurs. These two are retroperitoneal neuroblastoma and hydro- or pyelonephrosis. The neuroblastomata are not so very rare, in our experience, and resemble the embryoma in being rapidly growing, and often distort the renal pelvis. The points of

dissimilarity are that the neuroblastomata are commonly nodular, extend earlier to both sides of the spine, and do not displace the ascending or descending colon toward the midline as the embryomata usually do. However, there is no definite method of always differentiating between these two tumors before operation, nor is it essential to do so, as an operation is required in either case.

Hydro- and pyelonephrosis are also not rare in this age group, and are usually the result of urinary stasis from some congenital malformation. By palpation the hydronephrosis is less solid than the embryoma but this line of distinction is a narrow one at times. If palpation leaves one in doubt, intravenous or retrograde pyelography is clearly indicated. In a case where hydronephrosis is suspected the cystoscopic examination with retrograde pyelography and the collection of separate urine specimens are preferred to the intravenous method.

Ovarian tumors, enlargement of the spleen, omental cysts or duplications of the alimentary tract have sufficiently definite characteristics to make their differentiation possible. Among the rarer conditions malignant growth of the liver, congenital cystic kidney, or massive retroperitoneal embryoma, unattached to the kidney, may be difficult to rule out.

The diagnosis of Wilms' tumor having been made, the plan of treatment becomes the important question. Priestley and Broders,[5] Prather and Friedman,[43] Wharton,[44] Campbell,[16] and many others advocate preoperative irradiation for the purpose of shrinking the tumor followed by a nephrectomy, which is in turn followed by postoperative irradiation. In fact, this plan of treatment may be said to have become the accepted routine in many clinics. Roentgenotherapy usually reduces the size of the tumor very rapidly and thereby facilitates the operation. It does not, however, completely destroy the tumor. No patient, so far as I know, has ever been cured by irradiation alone, and I believe no specimen that has been examined following irradiation has failed to show viable tumor cells. Preoperative irradiation, if used, must be adopted for the purpose of facilitating the operation and reducing the operative mortality, or for preventing dissemination of the tumor.

At the Children's Hospital, in the last ten years, we have had only two operative deaths in 28 cases: an operative mortality of 7 per cent. One of these patients had a very extensive intra-abdominal metastasis at the time of operation and probably should not have been operated upon. The other apparently died of shock. I did not include, as an operative death, a patient who died of acute Streptococcus meningitis three weeks after a nephrectomy. The meningitis apparently had no connection with the surgical procedure. Of course, it is possible that preoperative irradiation with the attendant shrinkage of the tumor might have prevented the two operative deaths.

Does irradiation prevent dissemination of the tumor cells? So far as I know, there is no evidence that it does. On the contrary, we have impressions that it may facilitate the spread of the growth. It is the consensus that roentgenotherapy shrinks the tumor by destroying some of the cells but not all.

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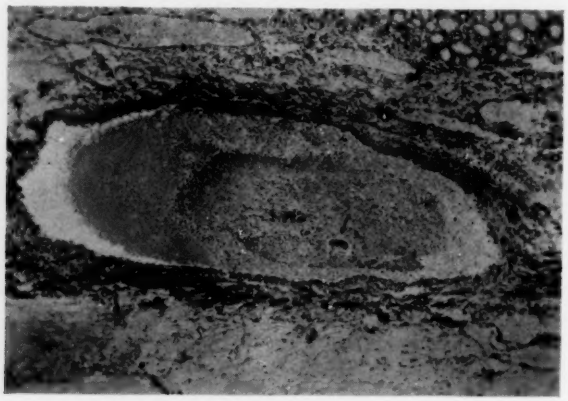

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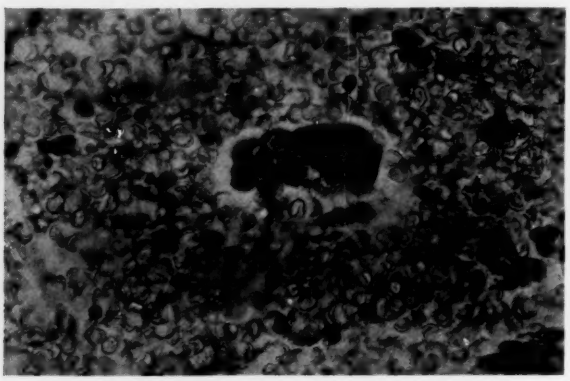

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Priestley and Broders[5] state that: "In the study of tumors removed at operation which were subjected to preoperative irradiation one may find an island of glandular or sarcomatous-appearing cells growing luxuriantly in the midst of necrotic débris the result of irradiation on surrounding cellular structures." Is it not probable that these living tumor cells may be picked up more readily by the blood stream after irradiation than before it? Our personal experience with preoperative irradiation is inadequate and is limited to but two cases. In one instance it was given for two weeks while waiting for the child to recover from a respiratory infection. The roentgenotherapy was very effective in shrinking the tumor. In this case the child had metastasis to the lungs three months after the nephrectomy and died in eight months with multiple metastases (Figs. 6 and 7). In the other instance, roentgenotherapy was advocated by the patient's uncle who was a doctor and was persisted in for four weeks,

FIG. 6 FIG. 7

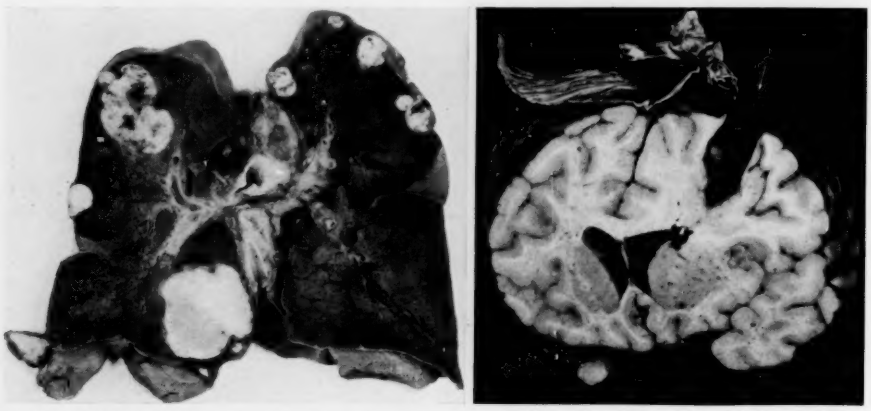

FIG. 6.—Photograph of the gross section of the lungs (A-37-162) of a patient who died eight months after nephrectomy of embryoma of kidney. Pre- and postoperative irradiation had been given. Note numerous metastases to both lungs.

FIG. 7.—Photograph of the gross section of the brain (9A-37-62) showing an extensive metastasis in the sulcus of the brain of the patient referred to in Figure 6. Note the hemorrhagic necrosis in the tumor.

at which time the child died before nephectomy was performed. This latter case was not included in the series of 45 cases, as there was a clinical diagnosis only.

Another fact for consideration is that the number of patients who have apparently been cured to date is not sufficiently large to draw definite conclusions in favor of one plan over another. The number of apparent cures, however, without the use of preoperative roentgenotherapy being greater than those with, suggests the advisability of resorting to operation without delay. As there is no known method of telling when the tumor invades the vascular system, it would seem logical to try to prevent this happening by performing a nephrectomy as soon as possible after the diagnosis is made. The size of the tumor is no criterion of the vascular invasion, as two of our smallest tumors showed the renal vein completely plugged with tumor cells at the time of the operation (Fig. 8).

Operative Technic.—The question of operability must necessarily be decided on various indefinite factors; the experience of the surgeon, the size of the tumor, and the general condition of the patient. In recent years, at the Children's Hospital, the size of the tumor has in no instance been considered a contraindication to operation. In some instances the weight of the tumor has been as much as one-fourth of the total weight of the child.

The patient is put in as good condition as possible for the operation by the administration of parenteral fluids and transfusion when indicated. In recent years the transperitoneal approach has been substituted for the former posterolumbar incision, as the latter does not give adequate room unless it is carried across the recti muscles and even then, if the tumor be a large one, the approach is less satisfactory. A rectus or a paramedian incision is the one we now employ. After the peritoneum has been opened, the ascending or descending colon, according to the side affected, is reflected toward the opposite side sufficiently to expose the renal pedicle and ureter. These structures are tied and cut before any attempt is made to mobilize the kidney. It is theoretically important to proceed in this order, particularly if the tumor is soft and broken down. The whole mass is then removed, great care being taken not to tear or rupture the capsule. It is probably wise to remove the perirenal fat, particularly along the renal pedicle, as it is here that lymphatic extension is most likely to take place. It is my belief that we have not been sufficiently thorough in this part of the operation at the Children's Hospital. After all bleeding points have been carefully controlled, the abdominal incision is closed in layers without drainage.

The postoperative care has consisted in the administration of parenteral fluids, adequate doses of morphine, and sometimes a transfusion. We have had no difficulty with the wounds made for the transperitoneal approach, even when they extended from the costal border nearly to the pubis.

Until very recently postoperative roentgenotherapy treatment has not been employed. Recently postoperative irradiation has been used on the theory that it may have greater effect on a small amount of tumor that may have been overlooked than on the original, or that some cells left may be of the type that can be completely destroyed by this treatment. The adoption of the present plan of postoperative irradiation is too recent for any evaluation to be made of it.

Prognosis.—It is extremely difficult from a study of the literature to draw conclusions as to the superiority of one form of treatment over another. This difficulty arises from the varied nomenclature of kidney tumors and from the lack of follow-up reports or confirmatory pathologic microscopic examinations. One gets the impression, however, from reading some 40 odd articles, that the operative mortality is very high and the late mortality is even higher. In the literature the reports of cures as the result of one form of treatment or another are so few as to be of only suggestive significance.

In a personal communication of November, 1937, Doctor Priestley, of the Mayo Clinic, informs me that they have obtained, apparently, four cures—one

of 17 years; one of six years; and two of three and one-half years' duration. Of these, one had no roentgenotherapy at all, and, including this case, three had no preoperative irradiation. Out of their four cures, only one had had preoperative roentgenotherapy. He had not evaluated the cases operated upon since 1934, and it is possible, of course, that these later results will alter the statistics. Campbell[16] reports one three-year cure that had had no preoperative irradiation and a 15-month cure that had had irradiation. Prather and Friedman[43] report one two-year cure following preoperative irradiation and nephrectomy, while Kretschmer and Hibbs[47] report one cure of one and one-half years' duration which had had nephrectomy only. Mintz[14] has recently reported seven cases of Wilms' tumor occurring in children at the Massachusetts General Hospital. These all died within six months after nephrectomy. Geschickter and Widenhorn[10] report end-results in 25 cases. They state that none of these cases were living at the end of five years, and most of them had died prior to two years after the nephrectomy. McCurdy[9] reports a series of 24 cases in which there were four operative deaths and a recurrence in the remaining 20. Eleven of these recurrences took place inside of five months. Thus, from the literature one may infer that there were eight probable cures, five of which had received no pre-operative irradiation.

In our series of 45 cases, there are 31 who have died. Of these 31, all but one had a recurrence or had died within one year of the operation. This fact has led us to feel that if a patient survives for more than a year and a half he can probably be regarded as a permanent cure. In the 28 patients operated upon during the last ten years, two died from the operation and 12 died later of the malignancy. Most of these showed evidence of recurrences within six months, and all died within one year after the operation. Of the 14 patients who are still living, 11 may be classified as probable cures, the length of time since nephrectomy varying from one and one-half years to 19½ years (Table I).

TABLE I

THE LATE RESULTS OF NEPHRECTOMY FOR RENAL EMBRYOMA
Without Preoperative Irradiation

Cases	Sex	Age	Nephrectomy	Well after Operation for
1	F.	5 mos.	Left	7 years+
2	F.	12 mos.	Right	10 years+
3	M.	5 mos.	Left	19½ years
4	F.	10 mos.	Left	3 years
5	F.	5½ mos.	Left	1½ years
6	F.	8 mos.	Right	1½ years
7	F.	7 mos.	Right	4¼ years
8	F.	31 mos.	Right	13 years
9	M.	10 mos.	Left	10 years
10	F.	5½ yrs.	Right	6¾ years
11	M.	22 mos.	Right	5½ years

The other three patients are not expected to survive. One is the patient mentioned before, who had bilateral tumors and who has had the larger tumor, that of the left kidney, removed, while the embryoma of the right kidney is being treated by roentgenotherapy. This tumor has shrunk so that it is barely palpable; the child looks very well; and has a normal N.P.N. four months after operation. The second patient has had a local recurrence which has been re-operated upon, and all the tumor which could be identified has been removed and the child is receiving roentgenotherapy (Fig. 12). The third patient is one in whom it was felt that all the tumor had not been removed at the time of the nephrectomy.

These 11 patients in our series, and eight cases taken from the literature, represent 19 probable cures of embryoma of the kidney. Of these 19 surviving patients, 16 received no preoperative irradiation, while three did. Of course, these numbers are not sufficiently large to be conclusive, but are they not suggestive? Considering the extreme malignancy of Wilms' tumor, and its very early metastasis, is not the chance of obtaining a cure greater by immediate operation than by delaying the operation for three to six weeks in order to shrink the tumor by roentgenotherapy before the nephrectomy is performed?

It is recognized that great strides have been made in roentgenotherapy in recent years, and that it is quite possible that our point of view may soon have to be changed. However, one may also hazard the opinion that it will be difficult to obtain uniform results by roentgenotherapy, on account of the extremely rapid growth, the early metastasis, and the very varied histologic picture which these embryomata present.

A brief summary of selected case reports from our series is appended:

Case 1.—I. J., female, age 5½, represents a six and one-half year cure following a transperitoneal nephrectomy without irradiation. She was admitted to the hospital June 22, 1931. One week previously, the mother had noticed a mass in the child's abdomen while she was giving her a bath. On close questioning, the mother stated that possibly the child had not had her usual hearty appetite during the past three weeks, but otherwise there were no symptoms.

Physical Examination.—She showed some pallor and was slightly undernourished, but there was nothing abnormal in her physical examination or in her laboratory studies except for the abdomen. This was asymmetric, with definite fulness over the entire right side and loin. There was an oval-shaped, firm, nontender, nonmovable, smooth mass, extending from just below the costal margin to the crest of the ilium. Its lateral border extended to the umbilicus, and posteriorly it filled the entire right loin. Its upper edge was separate from the liver.

Operation.—June 23, 1931: A transperitoneal nephrectomy was performed through a right rectus incision. The renal pedicle was clamped before an attempt was made to free the tumor. She had a fairly easy convalescence and was discharged on the twenty-first postoperative day with the wound well healed.

Microscopic Examination.—The sections were typical of a rapidly growing embryoma of the kidney.

Subsequent Course.—In January, 1938, six and one-half years after nephrectomy, her physician reported that she appeared to be in excellent health and had no signs of recurrence.

Comment.—A rather typical history of embryoma of the kidney with a six and one-half-year cure following a nephrectomy. This patient received no preoperative or postoperative irradiation.

Case 2.—H. A., female, age 7 months, represents a four year cure following a transperitoneal nephrectomy without irradiation. She was admitted to the hospital November 26, 1933. For the past four days she had had a nonproductive cough, fever, occasional vomiting, and constipation. The mother had noticed a mass in the right side of the abdomen one month previously, but at the time of the visit of the family physician this was thought to have been due to bowel stasis. The patient lost one-half pound in weight during the week previous to admission.

Physical Examination.—She was a fairly well developed but poorly nourished infant. She was somewhat cyanotic and her respirations were rapid and shallow. The veins of the chest and abdomen were visible. There was evidence of an upper respiratory infection with some bronchitis but no pneumonia. Temperature, 102° F. The abdomen was markedly prominent on the right side. On palpation a tumor was felt that filled the entire right flank. Its upper end was rounded and its mesial border was in the midclavicular line at its upper end, but extended to the navel at its midportion, and was to the left of the midline at its lower margin.

Operation.—December 4, 1933: A transperitoneal nephrectomy was performed through a right rectus incision, which extended from the costal border almost to the pubis. The renal pedicle was tied before the kidney was freed. She had an easy convalescence and was discharged on the twentieth postoperative day with the wound well healed.

Microscopic Examination.—This showed a typical right kidney embryoma.

Subsequent Course.—In January, 1938, four years after nephrectomy, the patient was reported to be in perfect health and to have no signs of recurrence.

Comment.—A four year cure of embryoma of the kidney with no preoperative or postoperative irradiation.

Case 3.—D. R., male, age 3, presents an early extension of the tumor into the renal vein and an unfavorable prognosis (Fig. 12). He was admitted to the hospital November 26, 1937. Four days before admission his mother noticed that he passed some dark colored urine and had some slight frequency during that day. There were no other urinary symptoms. One week before, he apparently had had some abdominal pain unassociated with vomiting, which had lasted for only one day. For the three days before entrance, he had had a rather constant, unproductive cough during the day. There was no fever, anorexia, vomiting, or constipation. He seemed to have no pain, was not fretful, and no physician was called. The mother brought the boy to the hospital for "examination."

Physical Examination.—He was well developed and well nourished, and in no apparent pain or distress. The abdomen appeared full in both upper quadrants. There was definite bulging in the right flank where a hard, smooth, nontender mass could be felt.

Operation.—December 3, 1937: A transperitoneal nephrectomy was performed through a right rectus incision. The renal pedicle was isolated, and tied before freeing the kidney tumor. The renal vein was dilated and firm to palpation and was ligated close to the vena cava. On section there was evidence of tumor extension into the renal vein. Except for the first three postoperative days he had an easy convalescence.

Microscopic Examination.—The sections showed typical embryoma of the kidney with intravascular extension. A section taken from the renal vein showed a rather thick-walled structure, the lumen of which was almost completely occluded by a large mass of tumor cells (Fig. 8). A section taken from the pelvis of the kidney including the adjacent portion of the tumor showed marked intravascular extension into the blood

vessels of the submucosa. There was, however, no extension of the tumor through the epithelium of the pelvis.

Subsequent Course.—Postoperative irradiation was carried out while the patient was convalescing in the hospital. He is now receiving roentgenotherapy in the Out-Patient Department. There was no evidence of metastasis that could be determined roentgenologically.

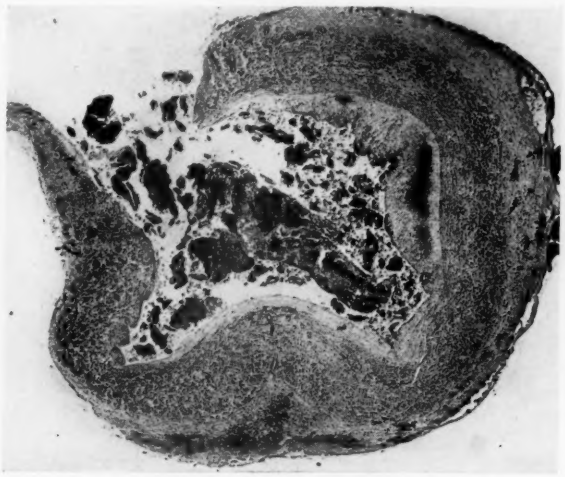

FIG. 8.—Case 3: Photomicrograph of section of embryoma of kidney (S-37-483) showing the renal vein filled with tumor cells extending from the main tumor. (Hematoxylin and eosin; ×18.)

Comment.—This case illustrates early vascular extension with the attendant unfavorable prognosis. It also illustrates one of the two cases of the whole series in which hematuria was a presenting symptom.

Case 4.—A. M. R., female, age 6½, who was the only bilateral case in our series and who had factors which made the diagnosis difficult. She was admitted to the hospital January 8, 1938, with a history of abdominal pain and fever of two days' duration.

Physical Examination.—Showed a moderately ill looking child. Temperature, 102° F. The general examination was negative except for the abdominal findings. In the left side of the abdomen there was a solid, smooth, rounded, nontender and nonmobile mass. This could be felt in the left costovertebral angle and extended forward almost to the midline and downward below the level of the umbilicus. On the right side, in the kidney region, there was a similar mass except that it was smaller and was tender in the costovertebral angle (Fig. 9).

Cystoscopic Examination revealed a very normal appearing renal pelvis on the left, the side of the larger tumor; while on the right the renal pelvis was distorted and displaced toward the midline (Fig. 10A and B). The urine examination showed a normal urine from the left kidney and some pus cells in that obtained from the right kidney. This case presented a difficult diagnostic problem.

Operation.—January 27, 1938: An exploratory operation was performed. Through a left rectus incision a typical embryoma, of large size, of the left kidney was seen. A left nephrectomy was performed. The mass in the right upper quadrant was a similar appearing tumor of the right kidney. In view of the grave prognosis, it seemed justifiable to obtain a biopsy specimen from the right kidney tumor.

Pathologic Examination.—Gross: The left kidney tumor weighed 690 Gm. (Fig. 11).

Microscopic Examination showed a typical embryoma. The biopsy of the right kidney tumor also showed a typical embryoma. *Pathologic Diagnosis:* Primary bilateral embryoma of the kidneys.

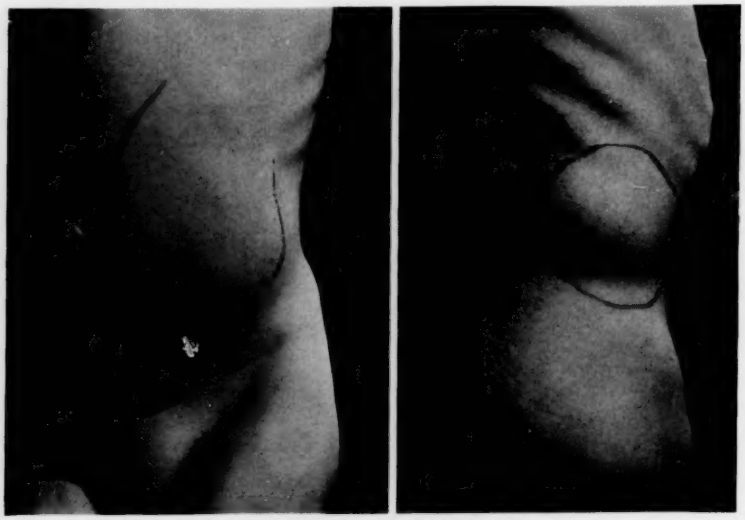

FIG. 9.—Case 4: Photographs showing the outline of the bilateral embryomata of the kidneys, the tumor of the left kidney being larger than the right.

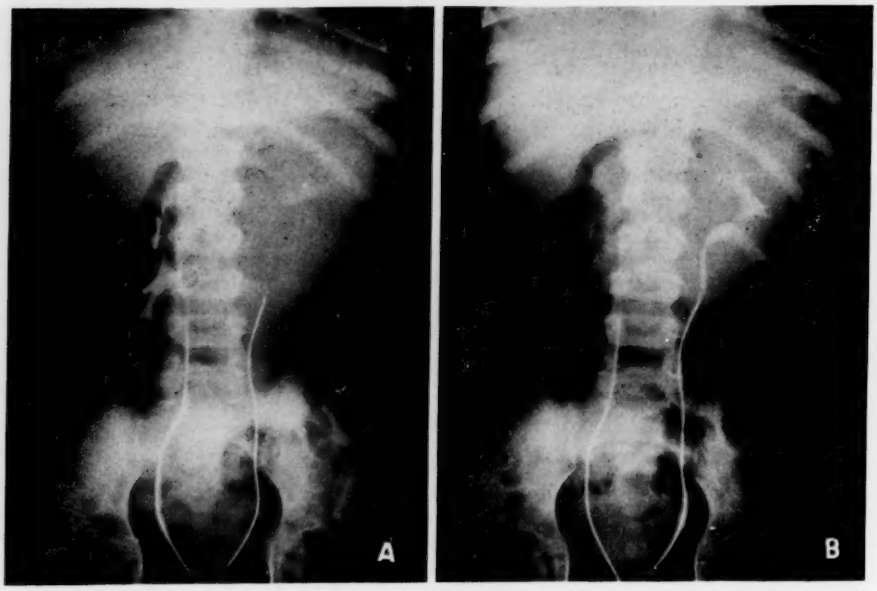

FIG. 10.—Case 4: (A) Retrograde pyelogram of the right kidney pelvis, the side containing the smaller tumor, showing it to be distorted and displaced mesially.
(B) Retrograde pyelogram of the left kidney pelvis, the side containing the larger tumor, which appears fairly normal.

Subsequent Course.—The child made a good postoperative recovery, and is now receiving roentgenotherapy for the right kidney tumor, which has decreased in size until it is barely palpable.

Comment.—This is the only bilateral embryoma of our series, and presented unusual difficulties of diagnosis. The normal appearance of the left kidney pelvis after retrograde pyelography and the tenderness in the right side were especially confusing. The prognosis is believed to be hopeless (Figs. 9; 10A and B; and 11). Ueda,[7] of Japan, reports a similar case in an eight months old baby in whom one kidney was extirpated and the child died seven weeks later. In the older literature, frequent mention is made of these tumors being bilateral, notably by Albarran and Imbert,[45] and Walker.[46] I have not found such frequent mention of bilateral occurrence in the recent literature.

Case 5.—J. M. R., female, age 5 months, illustrates an unusually large tumor, and recurrence and secondary operation following roentgenotherapy. She was admitted to the hospital October 19, 1937. For about two months the mother thought she had felt a mass in the abdomen. This had steadily increased in size. The child had not lost

FIG. 11 FIG. 12

FIG. 11.—Case 4: Photograph of the gross specimen of the embryoma of left kidney (S-37-31). The other kidney is also the seat of an embryoma. Note large tumor mass separated from the remainder of the kidney by a connective tissue wall. The tumor could not be separated from the rest of the kidney after removal. The cut surface of the tumor is divided into lobules of irregular size. Note small areas of hemorrhage and early necrosis, particularly beneath the capsule. Pelvis of this kidney appeared normal by retrograde pyelography (Fig. 10B).

FIG. 12.—Case 5: Photograph of the gross specimens of the several tumor nodules (S-38-81), which represent local recurrences removed at a second operation, four months after nephrectomy for embryoma of the kidney. Postoperative irradiation had been given.

weight and her only symptom in addition to the mass was that on two occasions during the past week her urine had been dark red in color. There also had been moderate constipation during the last week.

Physical Examination.—A well developed and slightly undernourished, rather pale child. The abdomen was asymmetric with a palpable mass in the left side. There was a smooth, nontender mass which filled the entire left side of the abdomen from the costal margin to the pelvic brim and extended across almost into the right flank.

Operation.—October 18, 1937: A left transperitoneal nephrectomy was performed through a left rectus incision. The renal pedicle was identified and cut. She had a fairly easy convalescence except for a slight separation of the skin at the upper end of the wound. Two weeks after operation she began to lose considerable weight and she

did not eat well, but following a transfusion she improved, regained some of her weight, and was discharged one month after operation.

Pathologic Examination.—Gross: The tumor weighed 1,058 Gm., which was practically one-quarter of the child's weight. *Miscroscopic Examination* showed a typical embryoma without vascular or pelvic extension.

Subsequent Course.—For one month after discharge the baby did well, gained four and one-half pounds in weight and was without symptoms. Two months after operation the baby began to lose her appetite and the mother noticed an enlargement in the left upper quadrant and felt a hard mass in this region. She returned to the hospital for further observation.

Physical Examination.—The abdomen showed a well healed scar. In the left upper quadrant a hard, smooth mass, about the size of an orange, was found which did not move with respirations and which extended back into the left flank. Its lower border was at the umbilicus. There was no tenderness and no spasm. Roentgenologic examination showed no metastasis in the lung, bone, skull or chest. Roentgenotherapy was given and the mass in the left quadrant became very much smaller until it became barely palpable. It seemed advisable to reexplore the patient.

Operation.—February 24, 1938: Through a left transverse incision, three to four rounded masses, measuring approximately 3 cm. in diameter, were found in the kidney bed (Fig. 12). These masses were bound to the surrounding structures, namely, the bowel, the lienorenal ligament and posterior abdominal wall. The tumor masses were moved intact. No loose necrotic tissue was noted, though the tumor itself was felt to be necrotic as the result of the roentgenotherapy. She had a rather difficult convalescence and even now we have considerable trouble with her diet and with effecting a gain in weight.

Microscopic Examination.—The specimen showed a recurrence of the embryoma of the left kidney. On the whole, the sections showed that the tumors were much less cellular, and less rapidly growing than the original one, but still contained viable tumor cells.

Comment.—This patient is still alive, five months after operation, and without further demonstrable metastasis, but the prognosis is considered extremely unfavorable.

CONCLUSIONS

After a study of 45 cases of embryoma of the kidney (Wilms' tumor) occurring at the Children's Hospital, and a partial review of the literature, the appended conclusions are suggested:

(1) That this tumor is extremely malignant and results in a very high mortality.

(2) That the operative mortality has been greatly reduced at the Children's Hospital in recent years.

(3) That the factors contributing to this reduced mortality are better preoperative preparation, better postoperative care, and better operative technic by the transperitoneal approach.

(4) That, to date, more probable cures have been obtained by immediate nephrectomy than by nephrectomy preceded by a course of preoperative roentgenotherapy.

(5) That it is possible that preoperative irradiation facilitates the operation and immediate operative mortality only at the sacrifice of an increased late mortality.

(6) That postoperative roentgenotherapy requires further trial before it can be evaluated.

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THERAPEUTIC MANAGEMENT OF URINARY INFECTIONS

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WE HAVE learned to interpret diseases of the urinary tract from the viewpoint of system-physiology and system-pathology, but we have not yet come to employ the concept of system-therapy to their treatment. This is particularly true in the case of urinary infections—where infection of one portion of the urinary tract may quickly involve other portions, or persist in spite of antiseptic therapy if there be faulty urinary drainage.

Any derangement of urinary transportion in any portion of the urinary tract, be it obstructive or functional, will cause infection to persist. In this respect infection in the urinary system differs *in its manifestation* from infections in other systems of the body.

As an introduction to the present discussion of the therapeutic management of urinary infections, we wish to present a group of cases which should be classified as therapeutic misdemeanors, because in each of these cases some of the underlying principles which should govern the therapeutic management of these infections were overlooked.

Figure 1 is a plain abdominal roentgenogram which shows the end-result of the faulty treatment of a Proteus infection in a patient who had but a solitary kidney. We see the left renal pelvis completely filled with stone. Due to the Proteus infection, the urine in this patient was persistently alkaline for a number of years in spite of all acidifying medications. In fact, the only time the urine became acid was immediately following a pelvic lavage with 1 per cent phosphoric acid. A plain roentgenogram taken two years previously showed the renal pelvis to be free of stone. During this two year period, however, a large amount of ammonium chloride was given in an attempt to acidify the urine. We know now that this therapy was wrong because the ammonium chloride was merely supplying a large amount of urea to the Proteus Bacillus for the liberation of ammonia which encouraged the precipitation of urinary salts. In this case, therefore, we see a failure of our therapy due to the administration of the wrong antiseptic as far as the infecting organism is concerned. We now know that the therapy of choice in Proteus infection is administration of sulphanilamide. But at the time when sulphanilamide could be obtained, it was already too late to influence the Proteus infection in this case, as the main prerequisite for success in sulphanilamide therapy, sufficient kidney function, was lacking.

Figure 2 shows the intravenous urogram of a patient who had been running a septic temperature for six weeks, with tenderness of the left lumbar region. It was difficult to correlate this excellent visualization of the left side with a septic pyelonephritis, particularly in view of the fact that only

occasionally did the urine show any appreciable amounts of pus. More frequently the urine was perfectly clear.

In this patient a retrograde pyelogram of the same kidney showed essentially the same picture as the intravenous urogram. Urine obtained from the ureteral catheter was perfectly clear. When we analyzed these two pictures, however, we realized that, because of good function on the intravenous urogram and the clear urine obtained through the ureteral catheter, it was impossible for this portion of the kidney to be the seat of a septic infection. The only possible explanation was a nonfunctioning, obstructed upper pelvis of this same kidney. That such was the case was proven when the kidney was

FIG. 1.—Plain roentgenogram showing end-result of faulty treatment of a Proteus infection of a solitary kidney.

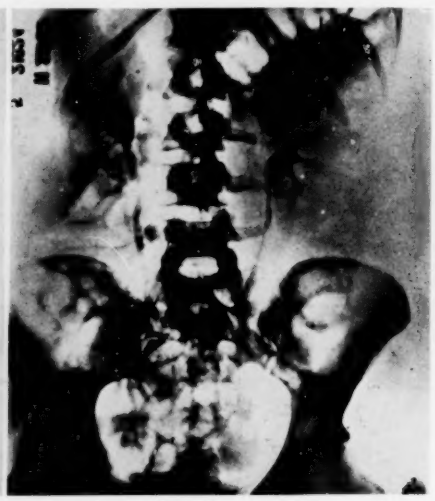

FIG. 2.—An intravenous urogram in an instance of a nonfunctioning obstructed upper pelvis.

removed at operation, the upper portion of which was infected, nonfunctioning and obstructed. All the urinary antiseptics administered had been excreted through the normally functioning portion of the kidney. In this case we see a failure of our antiseptic therapy due to a failure of elimination at the seat of disease.

Another problem was that of a man, age 29, with urinary infection plus urethral stricture. At no time had there been any upper urinary tract symptoms, but failure to influence this urinary infection by the various antiseptics, even after the urethral stricture had been sufficiently dilated, caused us to study the upper urinary tract, and in the urogram was demonstrated a full explanation of the reason for our therapeutic failure. It showed a ureteral obstruction on the left due to periureteritis, and inadequate renal function of the right kidney, probably due to the same cause.

Our next therapeutic misdemeanor was in a patient whose only complaint, in addition to his urinary infection, was vague gastro-intestinal discomfort. When the urinary infection did not clear up under the various antiseptics, a

plain abdominal roentgenogram demonstrated a suspicious shadow, which might have represented a calculus in the right upper urinary tract. An intravenous urogram showed a nonfunctioning right kidney, and the plain abdominal roentgenogram, taken with indwelling ureteral catheter (which met no obstruction in the ureter), showed the previous shadow to have moved to a higher position. To complete our diagnosis an air pyelogram was undertaken, which explained completely the failure of the previous therapy as far as the urinary infection was concerned; for here we had a case in which a stone acts as a ball-valve, at times obstructing the outflow of urine at the middle portion of the ureter, at other times resting in the renal pelvis, but at

FIG. 3.—An intravenous urogram of a female, age 33, showing the pathology consequent to subacute adnexitis.

FIG. 4.—An intravenous urogram of a male, age 31, showing a bilateral peri-ureteritis and ureteral dilatation, which has been influenced by adnexal infection.

no time causing typical symptoms of an obstructive uropathy, which, had it done so, would, of course, have caused us to make an earlier urographic study of the upper urinary tract. This therapeutic failure was due to delay in performing a complete urographic investigation.

With these illustrative cases as an introduction, let us now consider urinary infection in a more general way: Table I classifies the two principal groups of urinary infections. All infections of the upper urinary tract are secondary to infections elsewhere in the body and depending on their origin, these infections may be classified as (1) primary hematogenous, in which case they remain principally in the kidney, or as (2) urogenous, in which case the infection begins principally in the male or female adnexa but can involve the entire urinary system, producing dynamic disturbances of urinary transportation. Important for us to remember is that if only the peri-urinary structures are involved, the urine will not show any evidences of infection.

Let us take up these urogenous infections more in detail: Figure 3 shows the intravenous urogram of a woman, age 33, who had a subacute adnexitis of three months' duration. At no time were there any upper urinary tract symptoms. In the urine, however, could be found increased evidence of infection. After seeing the condition of the upper urinary tract, it was understood why an infection might persist. Antiseptic therapy was of no avail until the infected adnexa were removed and until, as a result of this, the upper urinary tract emptied itself more completely. Six weeks after a bilateral salpingectomy, a second urographic study showed a remarkable return to normal, and her urinary infection had practically disappeared.

TABLE I

CLASSIFICATION OF THE TWO PRINCIPAL GROUPS OF URINARY INFECTION

All infectious processes of the upper urinary system are secondary to infections elsewhere in the body

1. Primary hematogenous
   Remain principally in the kidney.
2. Urogenous
   Begin principally in male or female adnexa.
   Do not remain at portal of entry but involve entire urinary system.
   Produce principally *dynamic disturbances of urinary transportation.*
   If only the peri-urinary structures are involved the *urine* will not show *evidence of infection.*

The degree to which a restitution of normal physiologic emptying can be attained, in these cases of subacute adnexitis, is related quite definitely to the time element of duration. There is no rest to urinary function, though a very definite limit to reserve power, and if such an obstructive uropathy is allowed to continue, there follows greatly impaired renal function and a true infectious atony of the ureter with gross dilatation of it. Surgery is usually instituted too late to expect anywhere near a return to a normal emptying, and the ablation of the infection is, therefore, not to be expected.

Adnexal disease in the male is too infrequently thought of as a cause of impaired ureteral function and the basis for chronic urinary infection. Figure 4 is an intravenous urogram of a man, age 31. Long standing adnexal infection is expressing itself in a bilateral peri-ureteritis and ureteral dilatation. We have herein a complete corollary to that seen in the female, and it is becoming increasingly frequent as we study, by intravenous urography, cases of chronic prostatitis and seminal vesiculitis with persistent urinary infection. Unfortunately their cure is not so surgically brilliant as in the female, but to halt the advancing damage and destruction of renal function and to obtain a cure of the urinary infection depend upon a prompt recognition of the entire pathologic picture, with persistent and appropriate treatment. It is to be realized that such can progress to the same degree of utter derangement of renal function and a complete futility of all our antiseptic therapy.

TABLE II

POSSIBILITIES OF SEQUELAE OF ADNEXAL INFECTION

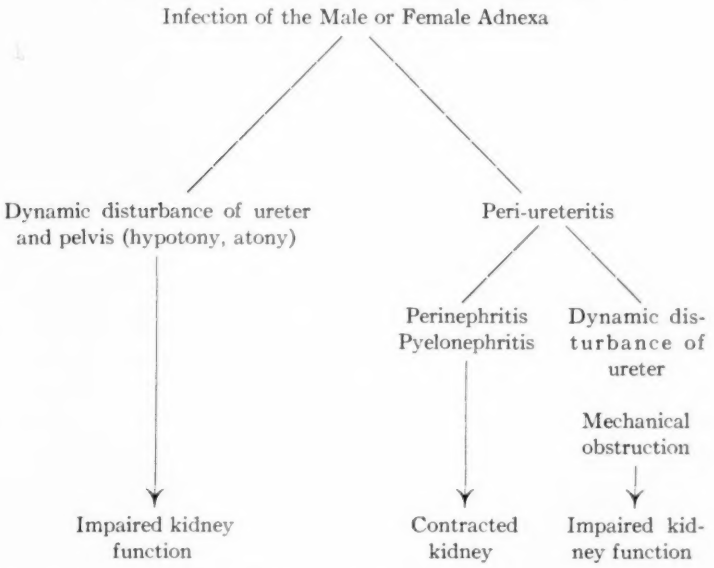

Table II shows a recapitulation of the various possibilities which might occur in infection of the male or female adnexa. The end-result, whether it be through dynamic disturbances or through obstruction caused by a peri-ureteritis, is, of course, the same—impaired renal function.

TABLE III

URINARY ANTISEPTICS

1. Oil of santal—Used by Chinese from remote times to treat gonorrhea.
2. Methenamine—Necessitates urinary p_H below 5.6 and concentration greater than 0.5 per cent.
3. Methylene blue
4. Acriflavine
5. Pyridium
6. Hexylresorcinol
7. Ketogenic diet
8. Mandelic acid
9. Sulphanilamide
10. New sulphanilamide substances

Let us now consider urinary antiseptics themselves: Table III gives a very incomplete list of those that may be administered orally, and of these we should consider only those beyond No. 6. We can also dismiss the ketogenic diet, when one realizes that urinary acidification is much more easily obtained by means of mandelic acid. We know that the action of mandelic acid depends on the concentration of the urine greater than 0.5 per cent and

a p_H less than 5.5. We therefore see that the success of mandelic acid depends entirely upon the function of the kidney. Mandelic acid is the antiseptic of choice in *Streptococcus faecalis* infection. Important in a negative consideration is the fact that mandelic acid therapy is useless in Proteus infection, as the p_H of the urine in these infections cannot be reduced to the acid side.

The antiseptic of choice, however, in all urinary infections, other than *Streptococcus faecalis,* is sulphanilamide. Marshall and his coworkers found that sulphanilamide is absorbed from the intestinal tract within four hours, and that, in administering a given daily amount of this drug in divided doses, it takes from two to three days to establish equilibrium between the amount ingested and the amount excreted. After equilibrium is established, almost 100 per cent of the daily ingested amount can be found in the urine in the free and combined form. Sulphanilamide is also excreted in the prostatic fluid, and this, of course, makes its use in the urogenous type of infection as invaluable as in the hematogenous type. Almost 50 per cent of the sulphanilamide is excreted in the urine as the inactive acetate. As the efficacy of sulphanilamide depends on the concentration in the urine, it is advisable in the acute urinary infections to limit the intake of fluids to approximately 1,500 cc. daily. In acute infections we have obtained the best results with the dosage scheme of 60 gr. a day for three days, with reduction to 40 gr. a day for another four days. But for therapeutic success we need sufficient kidney function. In those cases in which kidney function does not guarantee sufficient urinary concentration of sulphanilamide, we have found it useless to continue our therapeutic regimen beyond a week's time, as outlined above.

For chronic urinary infections, both hematogenous and urogenous, in which kidney function is not markedly impaired, we have not found it necessary to restrict fluids or to administer more than 40 gr. of sulphanilamide daily for a week's time. If there is no improvement in the chronic urinary infection at the end of this period, we are not likely to be therapeutically successful by continuing our therapy longer. We should then look for some asymptomatic obstruction to urinary drainage, or for some fault where failure is due to infectious destruction in whole or in part of a kidney.

Sulphanilamide possesses a great advantage over mandelic acid in that it is efficacious in alkaline urine. In fact, it is more effective in a slightly alkaline urine, as Helmholz has shown. This makes sulphanilamide particularly valuable in Proteus infections.

In summary, therefore, we may say that our therapeutic management of urinary infections calls for the use of mandelic acid in *Streptococcus faecalis* infections and the use of sulphanilamide in all other infections, but that the ultimate success depends upon three essential criteria, which must be known, namely: First, knowledge of the type of infecting organism; second, the presence or the absence of faulty drainage; third, that competent renal function conveys the appropriate antiseptic to the desired point.

DISCUSSION.—DR. BOLAND HUGHES (closing): When a substance such as sulphanilamide is introduced into medicine, one eventually passes through the stage of enthusiasm to that of confusion, confusion because following the original discovery, many allied substances are presented, each purporting, apparently, to possess some advantage over the original product itself.

We have been experimenting with several substances in the clinical investigation of urinary infections. Doctor Marshall has found di-sulphanilamide to possess a therapeutic index five times that of sulphanilamide itself. It is slightly less soluble in water but possesses the advantage of being excreted in the urine in the unaltered form. However, as far as urinary infections are concerned, we have found di-sulphanilamide to be superior to sulphanilamide only in pseudomonas infections. In a series of 53 cases treated with this substance, we found that two of our patients developed symptoms of peripheral neuritis. This, of course, indicates the great difficulty in transcribing, immediately, results as obtained from mice to man, because we can understand how difficult it might be to diagnose peripheral neuritis in the mice we infect and then treat with our drug.

We are also investigating the sodium salt of di-sulphanilamide. We have treated only 15 cases, and it may be that the sodium salt will not cause the symptoms of peripheral neuritis such as are obtained from the use of di-sulphanilamide itself.

However, no matter what urinary antiseptic we employ, be it either sulphanilamide or some new substance, which proves to be efficacious, we must recognize the three cardinal principles that Doctor Randall has mentioned in the present communication, namely: of knowing the infecting organism, of being certain that the kidneys function sufficiently to excrete the urinary antiseptic employed, and of correcting urinary stasis if present.

THYMOL THERAPY IN ACTINOMYCOSIS

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SO-CALLED lumpy jaw in cattle was first described by LeBlanc (1826), who, however, failed to understand its true nature. Although 50 years later Perronito (1879) claimed priority for the discovery of actinomycosis, he was antedated by Bollinger (Munich, 1877), who described a series of pathologic processes of the jaws and throats of cattle which had previously been considered as osteosarcoma, bone cancer and wooden tongue. Bollinger demonstrated the granulomatous nature of the condition and described detritus containing granulation cells, leukocytes, and opaque, yellow granular bodies which he regarded as true fungi. While these observations of the disease in cattle were being made, Lenert (1846) and von Langenbeck (1848) had described similar lesions in man. Later, James Israel (1879), working independently, recognized and described a fungus, found in a case of chronic empyema in a man, in which there was a large thoracic abscess present, as being similar to that found by Davaine (1859) and Bollinger (1877) in cattle. However, while these various studies concerning the "sulphur granules" in relationship to actinomycosis were frequently made, the botanist, Harz (1877–1878), was the first to call them ray fungus, or actinomycosis.

While such studies were mostly being made in Europe, John B. Murphy was the first (1885) to report an instance in a human being in the United States. About this same time Oscar Israel (1884) and Bostroem (1891) were making further observations as to the characteristics of the fungus. They found it to be aerobic. This concept, however, was overthrown by the work of Wolff and James Israel (1891), who demonstrated the cultures of Actinomycoses bovis to be anaerobic. This view, which was confirmed by Wright (1904–1905), is the one held at the present time, although the question is still not definitely settled. Liguieres and Spitz (1902) described the bacillary form.

Etiology.—While there is some confusion as to the nature of the organism and its variability, it is generally recognized that the anaerobic Actinomycoses bovis is most commonly responsible for the infection in man and appears to be the sole organism capable of producing the "sulphur granule." The only other organisms causing confusion are those found in instances of Madura foot (aerobic Actinomycoses farcinicus), a few scattered instances of the occurrence of the Actinobacillus, and Actinomycoses comitans found in four human cases in Zurich. Although there is much confusion in terminology in various grossly related pseudofungus forms and other terms, such as Nocardia and Streptothrix, which are frequently used, the term actinomycosis

is the oldest, best established, and most accurately conveys the character of the disease in man and in animals.

Transmission.—There are two common theories: (1) Exogenous theory.—The agent is considered a common parasite of the vegetable world living on grasses and cereals and is introduced by them mechanically. In some instances seeds and blades of grass have been found in the lesion. (2) Endogenous theory.—This is the most widely accepted. Since Actinomycoses bovis does not form spores, is anaerobic, and apparently grows only at body temperature, it could not exist in the plant world. The organism is occasionally present in the alimentary tract as the result of ingestion. Fragments of teeth are frequently found in actinomycotic lung abscesses; the disease occasionally develops in the knuckles after striking an adversary's broken tooth; or may develop following tooth extraction. Workers have isolated anaerobic strains of Actinomycoses from the mouth, tonsillar crypts and in the tartar around teeth. The botanical position of the fungus is still unsettled.

Diagnosis.—Although the diagnosis may be made from the tissues and microscopic sections, it is more easily and best made by examination from the pus from the discharging sinuses. The "sulphur granules" are readily recognized. They may be studied (a) as fresh preparations under the cover slip; (b) stain from mycelium; (c) may be cultured in various media.

Incidence.—Actinomycosis is a widespread disease occurring in all parts of the United States, being most common, however, in the Mississippi Valley and in the Northwest. The distribution corresponds somewhat to the dairy industry, and the association of man with cattle. It is most frequently found in males (80 per cent) between the ages of 20 and 30 years, with instances having occurred as early as 28 days and as late as 82 years (Sanford). Jacobson states that the cases are most commonly seen in the third and fourth decades. In the period between 1899 and 1906, Ruhräh collected 62 instances of actinomycosis in this country. In 1922, Sanford and Magath reported 96 at the Mayo Clinic, in addition to 119 found in the literature. In 1923, Sanford, in a careful review, was able to find a total of 678 cases in this country, but concluded that these probably represented only a small proportion of the true number.

Anatomic Location.—Although the disease process in man may be found in various parts of the body, as in cattle, the lesions are most commonly found in the head, and diminish in frequency as the caudal end of the body is approached. Accordingly, 60 per cent are found equally divided between the jaw, neck and face; 18 per cent are abdominal, including wall, peritoneal cavity, liver, intestine and appendix; 15 per cent are in the thorax, including the chest wall and the lungs, less frequently in the ribs and mediastinum; while only 8 per cent are found in the skin, and the disease is seldom found in bones other than the jaw.

Pathology.—Actinomycosis may be acute, subacute or chronic. It differs markedly from tuberculosis and syphilis in that it tends to remain localized and spreads only by direct continuity, its dissemination being largely due to

inhalation and ingestion. Its extension through the lymphatics is not recognized, but instances of rupture of the process into blood vessels with distant metastases have been reported. The lesion is initiated primarily, following the traumatic introduction of the organism, as a firm mass which gradually softens and breaks down. Various tissue planes are successively destroyed and replaced by granulation tissue, containing multiple abscesses. A very marked fibrous tissue reaction may occur, giving rise to a brawny induration of the skin overlying the lesion. However, the external aspect usually presents edema, erythema and multiple sinuses.

Microscopically the lesion appears granulomatous in nature but varies considerably according to the amount of secondary infection present. Typically, masses of radially branching mycelial filaments surrounded by lymphocytes and large mononuclear cells are seen. Beyond this a rather well marked fibroblastic reaction frequently containing giant cells is noted. Examination of the discharge reveals a thin, purulent exudate, usually containing the minute yellow "sulphur granules." The organisms are much more frequently demonstrated in the exudate than in the tissue.[15]

Treatment.—Although the etiology and the pathology have been known for some time, the futility of the treatment has always been recognized. Formerly it consisted of (1) radical surgery, drainage and curettement; (2) roentgenotherapy; (3) iodides in massive doses (400 drops of KI. t.i.d.); (4) copper sulphate, gr. ¼ (Bevan); (5) colloidal gold; (6) colloidal copper injections; (7) attempts at the elevation of metabolism by intravenous glucose with one unit of insulin for every 3 Gm. sugar; (8) methylene blue; (9) autogenous vaccine; and (10) nonspecific protein therapy. In recent years, however, this extensive array of methods has been simplified so that at the present time the following methods are employed: (1) Radical surgery, either alone or combined with iodides; (2) iodides alone; (3) roentgenotherapy; and (4) thymol with surgery.

Thymol Therapy.—Perhaps the greatest advance in the treatment of actinomycosis was made when the fungicidal action of thymol was first demonstrated by Kingery and Thienes[6] (1925), who reported a yeast-like dermatosis of the hands in fruit packing plant workers in the Northwest.

Myers and Thienes,[7] in June, 1925, treated a case of the above with 10 per cent alcoholic solution of oil of cinnamon. This oil was employed because of its efficacy against mold growths in preparations such as infusion of digitalis. Many cases were treated with this, and cinnamon water was used prophylactically. This led to investigation of comparative toxicities of several volatile oils and stereoptins on cultures of the pathogenic yeast responsible for these infections. Experiments with 12 volatile oils proved thymol to be the most efficacious in destroying the yeast. Following this experiment, a mixture of 5 per cent thymol and 2 per cent cinnamon was painted on sites of infections and appeared to effect rapid healing. Further employment of this mixture was made in instances of epidermophytosis infection of feet, pulmonary mycosis, low grade infections of extremities and finally in a case

of cervicofacial actinomycosis, which was treated with doses of thymol orally twice weekly, starting with 0.5 Gm. and ending with 1.5 Gm. with definite improvement.

Myers,[8] in 1927, further reported on "an unappreciated fungicidal action of certain volatile oils." He experimented with 22 volatile oils and found thymol and carvacrol, its isomer, the most effective both clinically and experimentally. A culture of actinomycoses proved readily susceptible to an aqueous solution of thymol but was resistant to the other oils. He concluded that powdered thymol in capsules by mouth was absorbed and circulated in sufficient strength to have pronounced fungicidal effect upon two patients with pulmonary moniliasis and one with actinomycosis; also he felt that localized, superficial mycotic infections may be treated with solutions of the oils and thymol in either alcohol or olive oil, in strengths compatible with the local irritability of the tissues.

Our method of procedure in the few cases has been to give orally 1.5 Gm. of powdered thymol in capsules two out of every three days; to open the sinuses widely, and to curette and fill them with thymol in olive oil (10 per cent solution); and then to inject the sinuses each day, small strips of gauze being inserted to keep them open.

CASE REPORTS

Case 1.—E. M., male, age 63, common laborer, was admitted to M. C. H. August 7, 1934, with a draining sinus in the right upper jaw which on entrance was thought to be due to an infected molar tooth. This was drained but continued to discharge. The patient was discharged but was readmitted September 25, 1934, with enlargement of the posterior aspect of the right side of the neck, having several draining sinuses under the right mandible. Eight days later the sinuses were curetted; on the same day thymol was started by mouth and the sinuses were injected daily with a solution of 10 per cent thymol in olive oil. At this time actinomyces were identified in the curetted material. The injections continued for ten days and given by mouth 21 days, when he was discharged. The patient received a total of 58.5 Gm. of thymol by mouth, or an average daily dose of 0.86 Gm. From the time of thymol treatment until discharge there elapsed a period of 51 days. He was followed in the Out-Patient Clinic for several months, and was reported clinically cured.

Case 2.—J. N., white, male, age 59, blacksmith, a habitual chewer of straw, was admitted to the hospital August 10, 1924, with a swelling under the right mandible. The diagnosis of osteosarcoma was made and high voltage roentgenotherapy was instituted. The lesion, however, continued to increase in size and on September 15, 1924, it was incised. Staphylococci were identified. However, the diseased condition continued to increase and on December 24, 1924, actinomyces were identified microscopically. Potassium iodide, up to 250 gr. a day, was given by mouth over a period of 58 days. This was then discontinued and thymol therapy, consisting of 1 Gm. by mouth twice weekly, was instituted. Seventeen days following the beginning of thymol therapy, the swelling had decreased markedly in size, and the dosage of thymol was increased to 1.5 Gm. twice a week. On April 25, 1925, the patient was discharged without evidence of a draining sinus. He, however, failed to return for check-up in the Out-Patient Clinic, so that the final outcome is not known.

Case 3.—A. S., male, age 45, farmer, was seen in April, 1925, with a discharging abscess under the left mandible, which he had noticed for two months. Actinomyces

were identified. Thymol, 1.5 Gm. in capsules on alternate days was administered. Within one month the lesion was completely healed and his family physician reports that there is no evidence of recurrence.

Case 4.—J. L. was first seen as an outpatient in St. Vincent's Hospital in 1930, with a draining abscess under the left mandible. Microscopic diagnosis of actinomycosis was made. Thymol was started by mouth and after a period of 12 weeks the lesion had completely healed without any evidence of recurrence.

Case 5.—E. H., male, age 30, farmer, was first seen in September, 1937, at which time he had three draining sinuses in the region of the left jaw. Six months previously he had gotten a "grass seed" lodged in his left ear; this was followed by a painful swelling in the left side of the neck. Removal of the grass seed afforded temporary relief of the pain but did not result in any change in the mass present. Three months later this mass was drained, resulting in the sinuses seen on admission to the hospital.

A large mass with several draining sinuses was present below the left mandible and in the region of the left parotid gland. The patient was unable to open his mouth more than about one-fourth of an inch at the incisors. The purulent material obtained from the sinuses showed typical "sulphur granule" bodies and actinomycoses were identified.

He was placed on thymol by mouth 0.5 Gm. t.i.d. for two consecutive days with one day of rest. This was continued for ten dosage-days, to a course which was then followed by a week's period of rest. The lesions showed no evidence of improvement. In November, 1937, the sinuses were widely opened and packed with gauze saturated in 10 per cent thymol in olive oil. Following this the tracts were again opened and curetted on five different occasions. Daily irrigations and packing the tracts with the above mixture were maintained. In February, 1938, due to slow progress, he was given a course of six roentgen treatments over the affected area. This was followed by marked but temporary improvement. Since that time several new abscesses have formed and been drained. At present he has six sinuses. Since the last surgical procedure the cavities have continually diminished in size and capacity. He has maintained the above schedule of oral administration of thymol to date with no apparent ill effects. His urine is normal.

Case 6.—Although not a case of cervicofacial actinomycosis, this case belongs to the cutaneous group, and is included through the courtesy of Doctors Hunter and Holden.

M. L., white, female, age 40, was first treated March 21, 1936, for an inflammation of the left shoulder, which was considered at first to be erysipelas; after several days it had spread rapidly toward the neck, the left breast, and then the left arm. On April 18, 1936, actinomyces were identified microscopically from the pus obtained. On April 21, 1936, the patient was placed on a regimen of 2 Gm. of thymol a day by mouth, and a 10 per cent solution of thymol in olive oil was injected into the sinus. The thymol dosage was decreased to 1 Gm. a day on June 21, and discontinued on August 24, 1936. On September 10, 1936, the sinuses were thoroughly curetted. These healed quite rapidly and there has been no further evidence of infection.

CONCLUSION

A review of previous methods of treatment as compared with the experience at the University of Oregon Medical School and St. Vincent's Hospitals, following the introduction of the use of thymol by Doctor Myers and his associates, as well as my own limited experience, leads me to the conclusion that the most effective present day treatment of actinomycosis is a combination of radical surgery with thymol.

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DISCUSSION.—DR. OWEN H. WANGENSTEEN (Minneapolis, Minn.): As Doctor Joyce pointed out, the etiology of actinomycosis is largely an enigma. There are those who insist that the disease is endogenous in origin, that is, that most of us carry about with us in health, organisms within our mouths which, under provocative circumstances, may give rise to the disease, actinomycosis. I do believe, however, that the majority of men who through experience and interest have acquired more than an ordinary acquaintance with the subject still subscribe to the old and more orthodox idea that the anaerobic Actinomyces bovis is the usual causative agent of actinomycosis.

Dr. A. T. Henrici, Professor of Bacteriology in the University of Minnesota Medical School, who as many of you know is an acknowledged authority of the higher fungi, has been kind enough to examine for me the material removed for diagnostic purposes or at operation from suspected cases of human actinomycosis. In all instances in which Doctor Henrici was able to establish the presence of actinomycosis he found that the cultural and morphologic characters of the organism were those of the anaerobic, gram-positive Actinomyces bovis.

As Doctor Joyce also pointed out, actinomycosis is essentially a granulomatous process in which the evidence of both an acute and chronic infection

occurs concurrently. Centrally areas of necrosis, liquefaction, and abscess formation may be found; more peripherally a proliferative reparative process occurs in which large collagenous fibers of connective tissue may be found—an attempt on the part of the host to arrest the spread of the disease. These areas of softening and induration are interspersed, which accounts for the brawny induration between and peripheral to the abscesses. The reddish violaceous appearance of the skin together with the unusual texture may give the impression of a carbuncle.

The anaerobic Actinomyces bovis live and thrive in the dead and dying detritus of the central areas of softening and abscess formation. The macrophages of the host constitute a means of spreading and extending the disease by carrying the organisms into adjacent healthy tissue.

With the consideration in mind that the areas of abscess formation, without blood supply and without oxygen, constitute an excellent medium for the perpetuation of the disease, it is quite obvious, I think, what the therapy indicated should be. The most direct method of attacking actinomycosis in man is to exenterate all the dead tissue by curetting it away. If that is done the spread of the disease will be arrested. The disease thrives only in tissues in which the oxygen tension is low.

When Doctor Joyce acquainted me, somewhat more than a year ago, with the experience which he and his colleagues had had with the treatment of actinomycosis with thymol, I was anxious to give the method a trial and tried to carry it out as he had used it. However, I was not so successful with its use as he, and after indifferent results in two cases, gave it up in favor of curettement.

Doctor Joyce reported the use of thymol in six cases of actinomycosis. In two of these, thymol had been used as the sole therapeutic agent; in the other four, surgery as well had been employed. It is, of course, quite significant that Doctor Joyce has been able to cure two cases of actinomycosis with thymol alone. In this connection it is to be borne in mind, however, that spontaneous fistulization alone succeeds occasionally in curing benign forms of the disease.

In the surgical clinic at the University of Minnesota, I set out, in 1929 and 1930, to determine which of the therapeutic agents which were in common use (surgery, potassium iodide, and irradiation) in the treatment of actinomycosis was most effectual. The experience of our clinic with a combination of these agents had not been a happy one. Surgical measures seemed to be the most direct approach, so I began with that method first. The results were so satisfactory and so much better than had been achieved by half-hearted surgery in association with oral administration of large doses of potassium iodide and external irradiation that I never got around to test the efficacy of these latter agents as sole therapeutic measures. Since 1930, therefore, all cases of cervicofacial actinomycosis have been treated by surgery alone. In the beginning, actinomycotic lesions were excised, but I soon learned that mere curettement and keeping the wound open by packing were just as effectual. During these years a large number of cases of actinomycosis have been seen and only one case of cervicofacial actinomycosis has died (ref. Table I, Case 3, ANNALS OF SURGERY, 752, 770, 1936). The lesion had extended through the orbit and auditory meatus into the meninges.

In most instances two curettements have sufficed. In one very extensive case (E. E. Univ. Hosp. No. 663102) involving the entire right side of the face and neck, six curettements were necessary. A few patients with chronic

granulomata, in which the diagnosis of actinomycosis could not be established, have been treated by curettement also, and with equal success.

Surgeons are no more objective than other medical men and though we find pleasure in wielding the weapons of our armamentarium in the practice of our art, yet should actinomycosis or any other disease prove equally or more responsive to treatment by nonsurgical means, I am certain surgeons would be the first to acknowledge the superiority of nonoperative treatment. Until such a remedy for actinomycosis is found, however, the most direct attack possible should be made upon the disease, namely, exenteration of the dead tissue.

I cannot conclude this discussion without saying something of potassium iodide, and roentgenotherapy in the treatment of actinomycosis. The use of potassium iodide originated from veterinary medicine. It has since been learned, however, that potassium iodide has no virtue in the management of real bovine actinomycosis. For actinobacillosis which causes "woody-tongue" in pigs and simulates actinomycosis closely from a pathologic standpoint, potassium iodide is a specific. Actinobacillosis, however, is apparently extraordinarily uncommon in man and its occurrence has been reported only twice.

Those of you who have followed the work of Heyerdahl in Oslo, employing roentgenotherapy in the management of actinomycosis, know that the method has merit. Yet the method appears to be valuable insofar as it promotes fistulization and encourages external drainage of the detritus in the diseased process. It is my impression that practically every case of cervicofacial actinomycosis can be cured if direct rather than dilatory approaches to the disease are employed.

THE PROBLEM OF WOUND HEALING

THE EFFECT OF LOCAL ANTISEPTIC AGENTS ON INFECTED WOUNDS

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THE history of the surgical art is replete with changing fashions in the management of wounds. At a time when the current practice demanded relentless, drastic treatment of wounds, Paracelsus aroused a conflict with the contention, "'Tis Nature healeth wounds, not meddling." Our knowledge of wound healing has improved vastly since the sixteenth century, but the conflict that developed at that time still remains unsettled. The state of antiseptic nihilism which existed prior to the World War[1] was followed shortly by a period during which the surgical literature was flooded with reports of new and different agents supposed to hasten the healing of wounds, and we are still in this phase of the cycle. The fact that there still exist differences of opinion as to the proper management of infected wounds is an evidence that the fundamental problems have not yet been solved.

It is the purpose of this communication to consider further the problem of wound healing, with particular reference to the effect of local agents upon infected wounds in man. Quantitative methods have been employed in this study, and clinical impressions, which are so often misleading, have been avoided.

The gross and histologic phenomena of wound repair are now well understood. The nature of the stimuli which initiate the mechanism of structural repair, and the factors, local and remote, which may alter the process are not so clearly understood. The reparative stimuli or growth-promoting substances which activate the structural mechanism of wound repair are, at least in part, the products of cell destruction, resulting directly or indirectly from trauma.[2] These substances, which are closely related to certain protein decomposition products, are elaborated by leukocytes and are abundantly present in embryonic tissue juices.[2, 3, 4, 5] The work of Hammett and Reimann,[6] Hammett,[7] Reimann,[8] Baker[9] and Birnbaum,[10] suggests that the growth-promoting hormone may be a chemical agent containing the sulphydryl group.

Whatever may be the exact nature of the reparative stimuli, and the forces which condition healing in a wound, it is important from a practical standpoint to understand the normal rate of healing in order to determine variables which may speed or retard tissue repair. Carrel and his associates afforded a quantitative approach to the problem from studies of the surface area of superficial, surgically clean wounds in man and animals. Carrel and DuNoüy[11, 12, 13] demonstrated that clean superficial wounds cicatrize according to a regular

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geometric curve, which may be expressed by a mathematic equation in function of area and time. The curves of wound healing which they presented, indicate that the rate of healing is proportional to the area of the wound and decreases with the age of the patient. These investigators also demonstrated the existence of a latent period, during which no decrease in the size of the wound occurs, normally varying from two to five days following the creation of the wound.[14] A latent period of four days from the time of incision to the abrupt onset of fibroplasia, has since been observed by Howes and Harvey[15] in an experimental study of gastric incisions in rats.

The latent period and the rate of healing after the actual onset of fibroplasia may be affected by many factors, local or remote. Arey[5] has recently reviewed the entire literature on this subject. A brief summary, however, of the factors which are definitely known to influence wound repair is appropriate to this discussion, in order that the many variables may be kept in mind.

Factors of a general nature, not applied or localized directly at the site of the wound, which may influence healing are: Age; diet; distant infection; and hormones. The experimental work of Carrel and DuNoüy[14] and the later observations of Howes and Harvey,[15, 16] have established the fact that the rate of healing is inversely proportional to the age of the patient. Howes and Harvey tested the tensile strength of gastric incisions in rats at varying intervals and noted the earlier onset of fibroplasia in younger animals. They could detect no difference in the velocity of healing, once growth had been initiated, although there was less tendency to retardation of repair in young animals. Carrel and DuNoüy, however, measuring the surface area of superficial wounds in man and experimental animals, observed a more rapid rate of cicatrization in younger individuals throughout the entire course of wound repair.

Clark,[17] using the technic developed by Carrel, found that a high protein diet shortened the latent period of superficial wounds in experimental animals, but did not influence the rate of healing after the onset of repair. On the other hand, Howes and Harvey[18] observed no difference in the length of the latent period in animals on a high protein diet, but the velocity of fibroplasia was increased and gastric incisions in rats attained a maximum tensile strength more rapidly. The above observations differ as to the exact phase of healing influenced by a high protein diet, but agree that a high protein diet shortens the total time required for wound repair, and that the course of healing is in some way influenced by protein metabolism. Recent work by Ravdin and Thompson[19] demonstrated the retardation of healing of abdominal incisions in dogs with experimentally induced hypoproteinemia. Normal healing was attained after restoration of normal serum protein concentration through the use of lyophilized serum.

Changes in the carbohydrate intake, according to Clark, do not influence the rate of healing of superficial noninfected wounds. Considerable experimental evidence exists, however, to indicate that high carbohydrate diet, and

disturbances in carbohydrate metabolism, unfavorably influence the course of cutaneous infections.[20] Absolute starvation did not appreciably alter healing in the experiments of Howes and Harvey,[15, 21] unless the nutritional balance was disturbed to such a degree that it, in itself, threatened survival.

Investigation of accessory dietary factors—the vitamins—indicates that vitamins A and C are of particular interest in relation to the problem of wound healing.[5] Avitaminosis generally tends to retard healing, and overdosage of vitamin D has been claimed to inhibit tissue repair, but the effects of vitamins A and C are more specific. An A deficiency, which has existed over a long period of time, delays wound repair. Treatment with vitamin A is said to accelerate healing under such conditions, even when employed locally, and may possibly influence healing in the absence of pronounced deficiency. The experimental and clinical studies of Lanman and Ingalls[22] indicate that vitamin C deficiency is of particular significance in wound healing. They demonstrated, quantitatively, lowered tensile strength of wounds in partially scorbutic animals and emphasized the fact that asymptomatic scurvy, detectable only by plasma determination of ascorbic acid, is of more importance in the healing of surgical wounds in humans than has been hitherto appreciated. These findings have recently been confirmed by Taffel and Harvey.[23]

Through clinical observations, and a few experimental studies, attempts have been made to correlate the functions of the various endocrine glands with tissue repair. No significant conclusions, however, can be drawn from the available data, other than that the possible effect of the endocrines must be considered in an occasional case wherein healing has been delayed.

Carrel[24] demonstrated that retarded healing may result from the presence of a distant infection experimentally produced, supporting a common clinical observation on the influence of remote infection on wound healing. There is some evidence to support the belief that general infections, particularly syphilis, retard healing irrespective of their influence on the general health of the patient.[25]

Infection, mechanical or chemical irritation, temperature and blood supply of the part, and local therapeutic agents must be considered as factors acting directly at the site of the wound which may influence healing. Carrel[26] demonstrated that experimental wounds in animals failed to heal when completely protected from local irritation. Mild infection and irritation initiate cicatrization, but gross infection or local trauma from mechanical or chemical irritation retard healing, according to the observations of Carrel[11] and Howes and Harvey.[15] Delayed healing from diminished blood supply is a familiar observation in occlusive peripheral vascular disease, whereas, increased blood supply and local temperature elevation favor healing of indolent ulcers.[5] Less attention has been directed toward differences in local blood supply of various types of tissue in relation to wound healing.

The effect of local therapeutic agents is more difficult to evaluate. Good results have been claimed for many forms of radiant energy, roentgen rays and other physical agents. Local application of hormones and vitamins has

been advocated. Stimulants containing the sulfhydryl radical, embryonic extracts, allantoin, and urea have all been proposed for local treatment of wounds. Numerous chemical agents, to be used as stimulants or antiseptics, are in common use, each having its own enthusiastic group of supporters. It is apparent from a survey of the literature that doubt must still exist concerning the claim of this horde of vulneraries because of lack of quantitative data. Many of the reports of common local therapeutic agents are merely enthusiastic clinical impressions. Studies based upon the healing time of a series of similar wounds do not take into consideration the many variables which may affect healing. A large majority of reports do not contain accurate bacteriologic studies. The early, incidental observations of Carrel,[11] and the recent critical work of Smelo,[27] are the only strictly objective studies that we have found on the subject of local therapeutic agents in relation to wound healing. Carrel[11] noted that gross infection retarded healing of superficial experimental and surgical wounds, and secured normal healing curves by using antiseptic dressings of dichloramine-T or Dakin's solution. Smelo, in a quantitative study of surgically clean wounds in man, observed the effect of many local agents, with particular reference to the supposed tissue stimulants. No local agent was found to influence the rate of repair in a consistent manner. He concluded that a wound will heal or fail to heal regardless of the material applied locally.

As many pertinent questions remain unanswered it is our purpose to consider further the quantitative effect of local agents, particularly the antiseptics, on the rate of healing and the bacterial flora of frankly infected wounds, whether superficial or deep. Is it possible to substantiate the frequently implied contention that antiseptics further repair by exerting a selectively greater effect on bacteria than on tissues? Is the chemical irritation from antiseptics in common use sufficient actually to inhibit the processes of repair by their lethal effect on the tissue cells? Will the topical application of any of the commonly used germicides actually result in wholesale destruction of virulent bacteria *in vivo*, and if so, will the change thereby produced in the bacterial flora appreciably alter the rate of wound healing? Will local agents, applied to the surface of a wound, prevent further tissue destruction and retardation of repair in the presence of infection with virulent, invasive organisms?

METHODS EMPLOYED.—In an attempt to ascertain the exact value of topical agents in the treatment of infected wounds, precise measurements were made of changes in the size and bacterial count of twenty wounds. The wounds studied differed in size, etiology and bacterial flora, but each was of the type regarded as surgically infected. It is important to stress the fact that all of the wounds under consideration were adequately drained. Improper drainage admittedly retards healing and evaluation of any methods of therapy in a series of infected wounds would be questioned if the sound principles of adequate surgical drainage had not been applied to all cases. The patients were in good health, unless otherwise stated, and every effort

was made to determine the presence of any factor, remote from the site of the wound, which may have unduly influenced the local changes. The dressing and management of these cases during the period of observation, and the quantitative studies of the wounds were carried out personally by the writer. Each wound treated with an antiseptic agent was dressed daily.

The surface area of superficial wounds was determined by the technic described by Carrel.[11] Since the writer was primarily interested in infected wounds healing by granulation, particular attention was directed toward changes in the volume of the wounds, rather than to changes in the surface area. Volume was determined by making a mold of the wound, using a sterilizable moulage which could be trimmed to conform to the contour of the body at the surface of the wound. The mold thus obtained could be easily removed, without trauma, and the volume determined with a minimal experimental error, even in deep wounds with overhanging edges. This method was used in a previous study reported from this laboratory.[27]

Quantitative bacteriologic study of these wounds presented a more difficult problem. Previous investigators of wound healing have contented themselves with occasional cultures or, at best, with bacterial counts by direct smear from the wound. Such direct smear counts are grossly inaccurate[28] and do not give a true picture of the bacterial changes in the entire wound. We have found not only differences in the bacterial count, but also variations in the type of organisms from smears or cultures in separate portions of the same wound. Washing the entire wound with a small amount of normal saline, the quantity being roughly proportional to the size of the wound, afforded a means of obtaining a fairly representative bacterial count. No attempt was made to compare the bacteriologic changes in different wounds, quantitatively, but the changes in any given wound, from day to day, could be followed with reasonable accuracy by using the same amount of saline for each washing. The decrease in the size of the wound as healing progressed would, in itself, tend to decrease the bacterial count of the standard volume of saline, and as a source of error would tend to favor the antiseptic agent. Hence, the failure of an antiseptic agent under investigation to decrease the count would further emphasize the impotence of that particular agent. The actual count was obtained by the dilution method, using as a rule one cubic centimeter of the washing from the wound, and employing dilutions of 1:4 through 15 tubes, with vigorous shaking between transfers. This technic is admittedly unsatisfactory for use in certain types of laboratory investigation,[29] but has proven satisfactory for our purposes in clinical use, where only gross changes are considered to be of significance. The dilution method also minimizes any effect, *in vitro,* of small portions of antiseptics carried over in the washings, and has the advantages of a technic which permits counting of only the living organisms. No deleterious effect was noted from the use of saline as the diluent, as is true in laboratory work,[28] probably because of the admixture of serum from the wounds. In spite of this, however, the washings from the wounds were not allowed to stand over two hours before

making the transfer to the culture media for the serial dilutions. Neopeptone, meat infusion broth, buffered to p_H 7.3, was used in all the dilutions. Final readings were made only after 48 hours of incubation, the logarithm of the dilution of the last tube showing growth being recorded. Dilutions were made in duplicate on cases early in the series, until it was well established that the technic afforded a method of study with little experimental error. Aerobic and anaerobic cultures, in broth and on blood agar plates, were made of each wound at the start of the period of investigation, in order to identify the types of organisms present. These were repeated whenever a change in rate of healing suggested the possibility of a qualitative change in the flora.

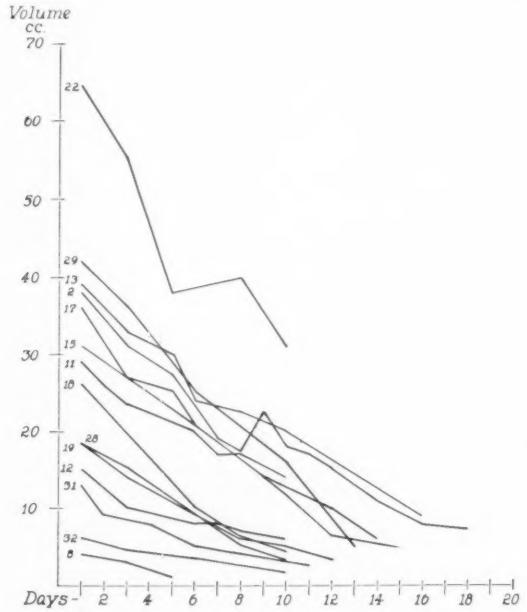

CHART 1.—Actual curve of healing as measured in cubic centimeters in the 14 cases where the rate of repair was considered normal.

RESULTS.—*Rate of Healing of Infected Wounds:* Precise measurements of either volume or surface area, or both, were carried out in 20 wounds of varied etiology. In many instances, studies were necessarily discontinued prior to complete healing because of the patient's discharge from the hospital, change in the type of dressing, or necessity for skin grafting. No cases have been included, however, which were not followed for a sufficient period of time to permit accurate observation of the course of healing. Topical agents used included dry gauze dressings, moist saline dressings, alcohol dressings, iodoform gauze, azochloramide 1:500 in triacetin, azochloramide in saline, merthiolate 1:1000, katadyn silver, Dakin's solution and zinc peroxide cream. Two cases received sulfanilamide by mouth. Aerobic and anaero-

bic cultures, together with bacterial counts by the method previously described, were made routinely.

The rate of healing was considered entirely normal, within the limits of experimental error, in 14, or 70 per cent, of the 20 cases. Two of the remaining cases had a normal curve of healing after prolonged latent periods of from six to eight days. The rate of healing by granulation, as determined by volume measurements, assumed a regular geometric curve parallel to the expected curve of healing as calculated by DuNoüy's[12] formula for the healing of superficial wounds. Chart 1 shows the actual curves of volume measurements in the 14 cases cited above, wherein the rate of repair was considered normal. In Chart 2, the actual size of a wound, as determined by both volume and surface area measurements, has been compared to the

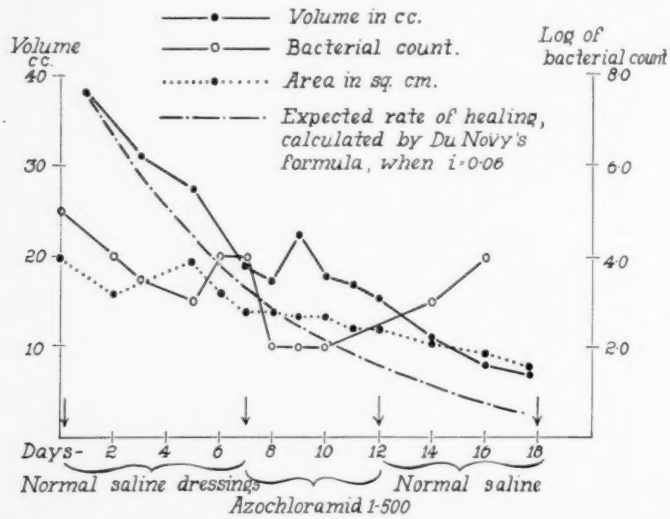

CHART 2.—Case 2: Actual rate of healing in a wound of the thigh, as determined by both volume and surface area measurements, compared with the expected curve of healing. The bacterial count was lowered with azochloramide dressings.

expected curve of healing. It is interesting to note the decrease in surface area of this granulating wound as compared to the volume changes. The early decrease in surface area occurred prior to actual epithelization and must be accounted for on the basis of contraction.[30] It seems likely, that the sharp vertical slope of the volume curve at the onset of healing may be due almost entirely to contraction, the actual rate of granulation remaining constant throughout the period of healing.

Wide variations in the degree and type of infection occurred in the 14 cases showing normal healing curves. As stated previously, all of the wounds were grossly infected, though adequately drained and without extensively undermined recesses. A review of the brief case summaries appended, will reveal that the causative organisms included the common bacteria found in surgical wounds. A few of the antiseptic agents, notably azochlora-

mide and iodoform packing, showed a definite tendency to lower the bacterial count in granulating wounds, and in such cases the clinical appearance of the wound was improved in that there was less exudate and less odor. The decreased number of bacteria and the improved clinical appearance of the wound apparently resulting from the local application did not, however, tend to stimulate healing. At the same time no deleterious effect on the rate of healing could be attributed to any of the agents employed locally. Wounds in this group healed at a constant, regular rate, irrespective of the bacterial flora or the topical agent used in the dressing.

Six of the 20 wounds in this series failed to heal at a normal, regular

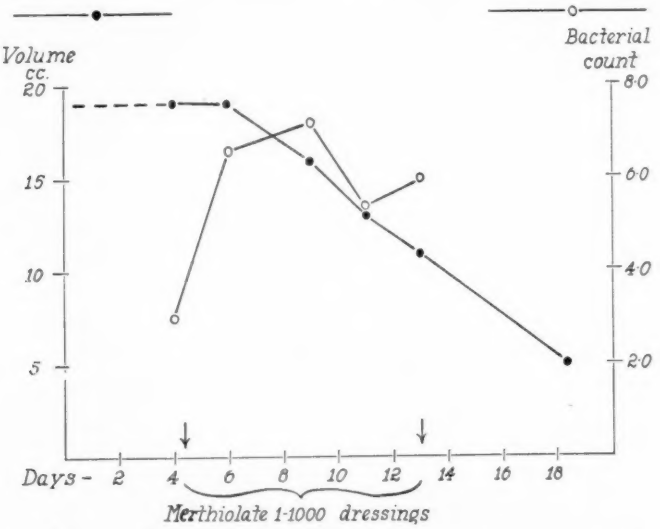

CHART 3.—Case 30: Prolonged latent period, apparently due to necrotic fascia at the base of the wound. The bacterial count increased, notwithstanding the application of 1:1,000 merthiolate dressings.

rate. Particular attention was directed toward the study of these cases for remote causes of delayed healing, but in only one instance was such a cause discovered. A latent period of six to eight days occurred in Case 9, a female, age 60, with moderately severe diabetes. In the remaining five cases the delayed healing must be attributed, insofar as can be determined, to local causes. The two wounds studied in Case 1 presented a clinical picture and bacteriological findings similar to the type of chronic progressive undermining ulceration, which has been described by Meleney[31, 32] as due to the microaerophilic, hemolytic Streptococcus. The progressive lesion, and failure of normal healing in such cases is due to a specific, locally invasive type of infection with continuing tissue destruction. Normal rate of wound healing in this case did not occur until a radical excision and treatment with zinc peroxide had been instituted.

The three remaining wounds in the group, where repair was retarded, varied in etiology, location and bacterial flora. The presence of devitalized,

necrotic fascia, affording a foothold for invasive organisms, was a factor common to all of these wounds, which undoubtedly delayed wound repair. The wound in Case 30 (Chart 3) was relatively clean, being only mildly infected with nonhemolytic *Staphylococcus aureus*. A latent period of 8 days was observed in this wound, during which time necrotic fascia at the base of the wound remained exposed and granulation did not progress. Normal granulation occurred after the fascial slough had completely sep-

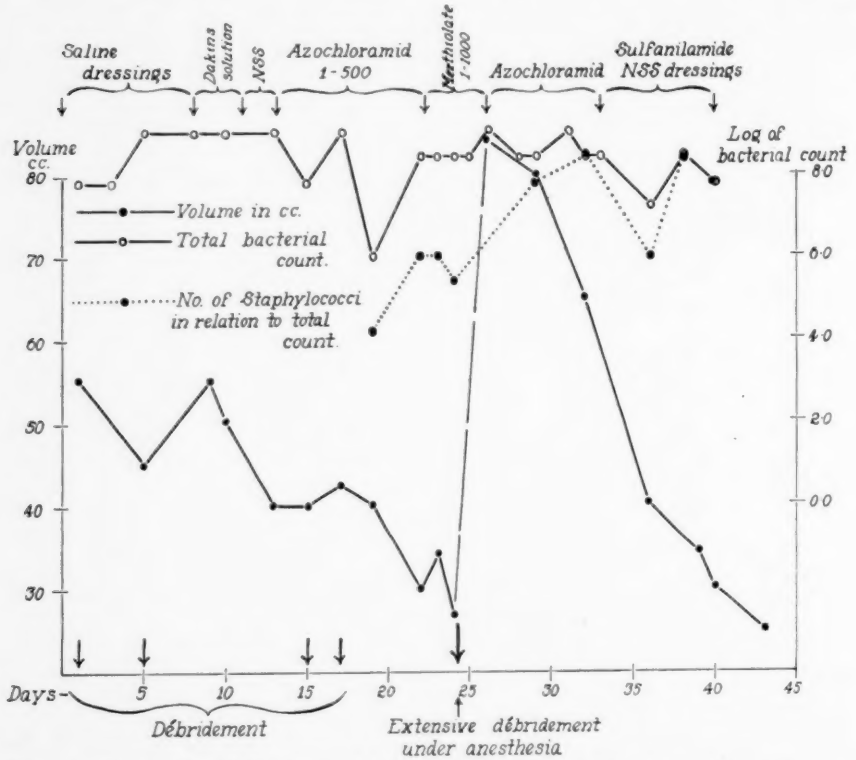

CHART 4.—Case 25: Retardation of wound healing, due to fascia necrosis with persistent infection. The bacterial count was not influenced by antiseptics.

arated, although an actual increase in the bacterial count took place. A similar course of events occurred in Case 14, a wound grossly infected with hemolytic *Bacillus coli*. The complete curve of healing of the third wound, Case 25 (Chart 4), demonstrated a retardation of healing during the period of fascia and muscle necrosis in a wound infected with *Streptococcus hemolyticus* and *Staphylococcus aureus*. The rate of repair in each of these three cases approached the normal expected curve of healing only after mechanical débridement or natural sequestration of devitalized tissues. The subsequent course of healing, then, did not differ from that observed in the cases cited above in which there was no excessive tissue necrosis and no retardation of repair.

The Effect of Topical Agents on the Healing of Infected Wounds: Studies of the effect of topical agents on the bacterial flora were conducted in a total of 23 cases. The technic employed has been previously described. Complete studies of the rate of healing were conducted in 20 of these cases.

The agents used locally may be divided into two groups: (1) Admittedly inert materials—dry gauze and moist saline dressings. (2) Antiseptic agents —azochloramide 1:500 in triacetin, azochloramide in saline, 70 per cent alcohol, merthiolate 1:1000 aqueous solution, Dakin's solution, katadyn silver,

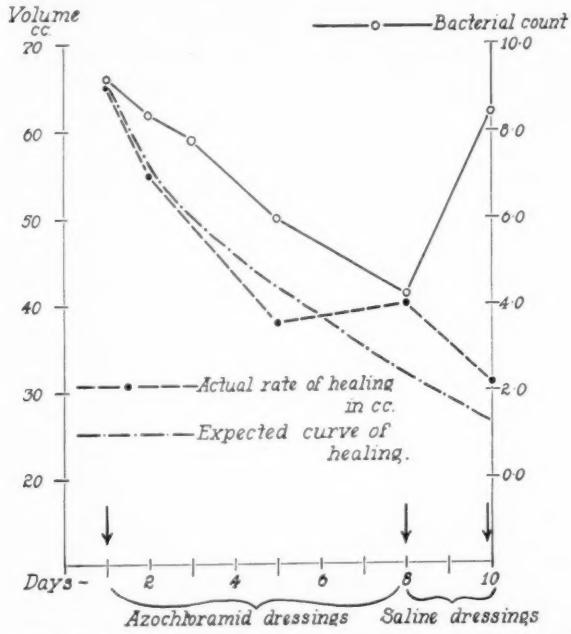

CHART 5.—Case 22: Favorable influence of azochloramide on surface infection of a normally granulating wound.

2 per cent acetic acid and zinc peroxide cream. In two cases sulfanilamide was administered by mouth.

In the group of granulating wounds which were free of necrotic tissue, azochloramide and iodoform gauze did influence the bacterial counts. Charts 2 and 5 show representative curves of the logarithm of the bacterial count in such cases. The diminution in the number of organisms, however, was not associated with rate of wound healing above the expected normal. In wounds containing sloughing tissue, no appreciable change in the bacterial content was observed with the use of any topical agent (Charts 3, 4 and 6). Clinical improvement and a normal rate of healing were observed after the use of extensive débridement and zinc peroxide cream in two chronic burrowing ulcers. Quantitative bacterial counts were not attempted during the period when zinc peroxide was employed, because of technical difficulties, so that the exact effect of this agent on the degree of infection cannot be

definitely determined. Two per cent acetic acid, applied at frequent intervals, lowered the bacterial count of *Bacillus pyocyaneus* in two cases under observation, although the total bacterial count remained unaltered, because of the presence of a mixed infection with *Staphylococcus aureus*.

With the above exceptions, no topical agent had any appreciable effect on the bacterial flora of the wounds in this series. It may further be stated that, with the exception of zinc peroxide in infections where it is specifically indicated, none of the agents studied had any beneficial action on wound healing. The few antiseptics which influenced the bacterial counts in relatively healthy granulating wounds had no effect in the presence of tissue necrosis, which seemed to be constantly present whenever a wound increased in size or failed to heal because of a local factor. We think it advisable,

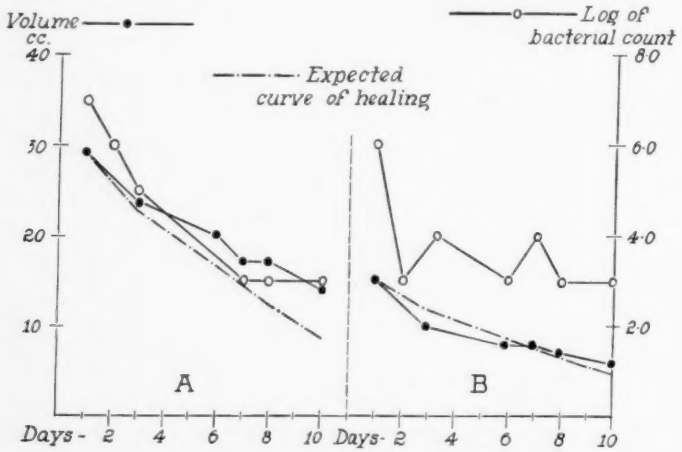

CHART 6.—Case 11: Bilateral infected wounds. Wound A, was treated with normal saline, and Wound B, with azochloramide for the first six days, with no appreciable difference in the bacterial counts of the two wounds.

however, to call attention to the action of one of the agents in this group; namely, Dakin's solution, which was used at two to three hour intervals for three days in one case without appreciable influence on the bacterial count (Chart 4). The action of Dakin's solution on necrotic tissue,[33] affords a means of chemical débridement of a wound which is not possessed by the more stable chlorine antiseptics. It seems to me that this action, peculiar to Dakin's solution, may account for the fact that it is outstanding as a local agent which has survived the test of adequate clinical trial for over 20 years. Is it not possible that Dakin's solution shortens the healing period of dirty, sloughing wounds by hastening the separation of necrotic tissue, and not by any direct antiseptic action? Further speculation, based upon the critical study of this series of cases, and impressions gathered from other cases which were not suitable for quantitative study, persuades us that other specific local agents, notably zinc peroxide, which have received favorable clinical trial, may exert their action by creating an unfavorable environ-

ment for bacterial multiplication, rather than by any wholesale destruction of the offending organisms.

It is not our purpose to consider the action of general agents on wound healing, but the use of sulfanilamide in two wounds infected with *Streptococcus hemolyticus* afforded an interesting observation which warrants mention. The drug was administered by mouth at six hour intervals throughout the 24 hours to two patients, similar total doses being used in each case. In Case 28, a pure culture of hemolytic Streptococcus was obtained at the time of drainage of an abscess of the thigh. Sulfanilamide therapy was started within a short time of operation. A culture, taken 36 hours after the treatment, was started and all subsequent cultures, aerobically and anaerobically, were negative for Streptococci, although a secondary invader was cultured. In Case 25, sulfanilamide therapy was employed five weeks after the drainage of an abscess of the lower leg, at a time when the wound contained necrotic tissue and was grossly infected with *Streptococcus hemolyticus* and *Staphylococcus aureus*. The sulfanilamide had no appreciable effect on the Streptococci in this wound, either because the organisms, lodged in dead tissues, could not be reached by the sulfanilamide present in the tissue fluid, or because the presence of necrotic tissue interferes with the action of sulfanilamide on Streptococci.[34]

SUMMARY OF CASE REPORTS

Case 1.—J. C., age 47: Small ulcer over the inner aspect, left lower leg, with blebs over the external malleolus. Treated for three weeks with hot dressings, sulfanilamide, roentgenotherapy and gelatin boots over alternate periods without improvement. Edges of the ulcer curled, irregular and undermined with "daughter ulcerations" beyond the periphery. The ulcer was painful and tender to touch.

Culture: Hemolytic Streptococcus and *Bacillus coli.*

The ulceration continued to spread, in spite of the treatment noted above. Excision and treatment with zinc peroxide was followed by improvement though normal healing, as determined by skin area measurements, did not occur until five days after a second, more extensive excision of the undermined skin edges. Successful pinch grafts were obtained two weeks after radical excision and zinc peroxide treatment.

A similar, though smaller, chronic, progressive ulceration of the right lower leg was followed with skin surface area measurements for one week, without showing any tendency to heal. Radical débridement, zinc peroxide dressings and skin graft afforded an effective means of initiating healing.

This patient's general health and nutritional status were good. Blood sugar was normal and Wassermann was negative.

Case 2.—A. S., age 13: Granulating wound of the left thigh extending down to the fascia lata; following surgical incision and drainage of a subcutaneous abscess.

Culture: Hemolytic *Staphylococcus aureus.*

Dressings were started six days after operation, at the time of removal of an iodoform pack which was placed in the incision at operation. Normal saline and azochloramide 1:500 in triacetin, were used locally over alternate periods.

Case 8.—J. McC., white, male, age 34: Infected herniorrhaphy wound. Lower angle of the incision opened down to the external oblique fascia and measurements started 24 hours later.

Culture: Staphylococcus aureus.

Moist normal saline dressings. Healing was normal, and the latent period of less than 24 hours' duration.

Case 9.—H. C., colored, female, age 60: Surgically clean wound of the back following excision of a small carbuncle.

Culture: Staphylococcus aureus.

Patient was a severe diabetic, controlled by diet and insulin. Nutritional status and general health were otherwise good. The latent period was six to eight days' duration, with normal healing curve thereafter.

Case 11.—L. P., white, male, age 66: Bilateral wounds of the buttocks following surgical incision and drainage of localized abscesses; resulting from the intramuscular injection of medication.

Culture: Staphylococcus aureus obtained from both wounds.

Dressings started 24 hours after incision and drainage. Alternate dressings of normal saline and azochloramide 1:500 in triacetin. Normal healing occurred, with no demonstrable latent period.

Case 13.—T. K., white, male, age 37: A wound of the back following surgical excision of a large carbuncle. Measurements started six days after the operation, at which time the edges of the wound were necrotic and sloughing and there was an area of necrosis at the base. The wound was superficial to the fascia.

Culture: Staphylococcus aureus.

Dressings of normal saline packs and azochloramide 1:500 in triacetin, over alternate periods, changed at 48-hour intervals. Normal healing occurred.

Case 14.—E. F., white, male, age 60 to 70: Infected incision following appendicectomy, with drainage. Incision opened widely, two weeks after operation, because of infection and undermining, and measurements were started at that time. Slough and necrosis involved the fascia of the external oblique.

Culture: Bacillus coli and diphtheroids. The culture was repeated three times during the course of study.

Dressings of normal saline and merthiolate were employed over alternate periods. Nutritional status and general health were good except for mild anemia. Red blood cells, 3,900,000. Blood sugar and urea, normal. Kahn, negative. Serum proteins, normal. Delayed healing was noted by volume measurements and infection was not controlled by the antiseptic dressings.

Case 15.—L. O'K., white, female, age 14: An incision of the left lower leg following surgical removal of the lower one-third of the left fibula for chronic, recurrent osteomyelitis, localized to the fibula.

Culture: Staphylococcus aureus.

Measurements were started one week after operation, at which time the iodoform packing was removed. Dry dressings, azochloramide 1:500, and merthiolate were employed over alternate periods. General condition was good except for anemia (red blood cells, 2,000,000 to 3,200,000 during the course of the study), which was treated by transfusion prior to onset of the study. Wound healing was normal.

Case 17.—M. P., white, male, age 46: A wound over the lower right thoracic cage anteriorly, following resection of the ninth and tenth costochondral junctions for osteomyelitis, resulting from a previous transpleural drainage of an amebic liver abscess. Dressings started four days after operation. Merthiolate, azochloramide and normal saline were employed over alternate periods. Normal wound healing resulted.

Case 18.—P. W., colored, male, age 49: A wound resulting from incision and drainage of a localized abscess about a silk suture, in the external oblique fascia. The abscess drained two months after the original operation, a herniorrhaphy. There was marked inflammatory edema and local phlebitis of the tissue surrounding the abscess. Roentgenotherapy of 100 R. was used four times prior to the incision and drainage. The patient's general condition was good.

Culture: Staphylococcus albus and *aureus.*

Dry dressings and katadyn silver were used. Normal healing occurred.

Case 19.—H. B., colored, male, age 38: Localized abscess of the buttock in which dressings were started three days after incision and drainage.

Culture: Bacillus proteus and hemolytic *Staphylococcus aureus.*

Dressings of katadyn silver and azochloramide during alternate periods. General condition of the patient was good except for empyema thoracis, adequately drained. Wound healing was normal.

Case 22.—J. T., white, male, age 32: An infected right lower rectus surgical incision following exploratory celiotomy. Measurements started 36 hours after the incision was opened.

Culture: Staphylococcus albus and *aureus.*

Dressings of normal saline, azochloramide and 70 per cent alcohol were employed. Healing was normal.

Case 25.—W. S., white, male, age 54: A cellulitis of the right lower leg, secondary to infection of the great toe, with extensive muscle and fascia necrosis at the time of operation. Further débridement performed one week following original incision and drainage. Study was started at this time. General health was good.

Culture: Streptococcus hemolyticus and later secondary infection with *Staphylococcus aureus.*

Dry dressings, Dakin's solution, azochloramide, merthiolate and sulfanilamide were employed. Normal healing did not begin until 29 days after the beginning of the study.

Case 28.—J. S., white, male, age 60: A superficial abscess in the anterior surface of the thigh, secondary to a streptococcic infection of the toe.

Culture: Streptococcus hemolyticus.

Dry dressings and sulfanilamide per ora were used. Normal wound healing resulted.

Case 29.—M. S., white, female, age 50: A wound of the back following surgical excision of a cutaneous neoplasm. General condition was good.

Culture: Bacillus proteus and *Staphylococcus aureus.*

Dressings consisted of iodoform packing changed every 48 hours, and dry gauze packing. Normal wound healing resulted.

Case 30.—A. G., white, male, age 44: A right subcostal incision for a cholecystectomy, with disruption of the wound down to, but not including the fascia, though the fascia was exposed and was necrotic, the wound was surgically clean.

Culture: Staphylococcus aureus.

Dressings of merthiolate 1:1000 were employed throughout the study. There was a latent period of six to seven days, after which healing progressed at a normal rate.

Case 31.—M. Q., white, male, age 62: A decubitus ulcer of the sacrum, extending down to the muscles, on which dressings and measurements were started 24 hours after débridement and excision. Iodoform gauze dressings were employed. The wound repair was normal.

Culture: Staphylococcus aureus and *Bacillus proteus.*

Case 32.—F. V., white, male, age 51: A decubitus ulcer over the lower back, which was thoroughly débrided. Normal healing occurred.

Culture: Staphylococcus aureus.

SUMMARY AND CONCLUSIONS

It is apparent from the above observations that the majority of infected wounds, adequately drained and not containing sloughing tissue, in normal individuals, will heal according to a regular geometric curve, the rate being proportional to the size of the wound and decreasing with the age of the patient, regardless of the type of local treatment. Infection with invasive organisms in the presence of extensive necrosis and the presence of dead

tissue in the wound, even without active infection, are the outstanding local causes of retarded healing. This is in accord with the statement by Arey[5] that: "In open wounds, which are healing by granulation, the formation of fibrils depends on the prevailing metabolic conditions. While the destructive phase is still in progress, fibrils are not formed. In a similar manner regions of necrosis or areas containing foreign bodies and rich in bacteria have an abundance of cells and are thus not favorable to fibril development. Only when all dead and foreign material is removed, either by enzymic digestion, phagocytosis or sloughing, does fibril formation progress."

The group of local agents considered in this study had little, or no, beneficial effect upon the healing of infected wounds, except for the action of zinc peroxide in specific cases. The few antiseptic agents which had definite bactericidal action on surface organisms in normal granulating wounds were ineffective in the presence of tissue necrosis, and it is only under the latter circumstances that the existing infection is likely to retard healing.

(1) Healing of granulating wounds under normal conditions, as determined by precise volume measurements, occurs according to a regular geometric curve which may be expressed, in function of area and time, by the mathematic equation presented by Carrel and DuNoüy for the normal cicatrization of clean surface wounds.

(2) The presence of a large number of organisms on the surface of wounds does not ordinarily retard healing. Specific types of infection with invasive organisms, and the presence of necrotic tissues and inadequately drained areas of infection, are the outstanding local causes of delayed repair.

(3) A quantitative study has been made of the effect of local agents, particularly antiseptic substances, on the rate of healing and the bacterial flora of infected wounds. The following conclusions may be formed on the basis of this objective investigation of a limited number of commonly used vulneraries:

(A) Topical agents will not prevent further tissue destruction and retardation of repair in the presence of infection with virulent, invasive organisms by any direct antiseptic action. The few antiseptics, which decreased the number of surface organisms in wounds healing at a normal rate, were ineffective in the presence of tissue necrosis, and exerted no beneficial effect on the rate of wound repair.

(B) No evidence was obtained to indicate that any of the agents in this series retarded healing by excessive chemical irritation of tissue cells. There is, then, no apparent contraindication to the use of antiseptic dressings in the prevention of infection in surgical wounds.

In the management of infected wounds, less attention should be given to the selection of a potent local antiseptic agent. It is of more importance to consider the problem of increasing local tissue immunity, which may be influenced by factors of a general nature remote from the site of the wound, and aiding the sequestration of necrotic tissues rich in bacteria by mechanical or chemical débridement and adequate surgical drainage.

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THE EFFECT OF URINARY BLADDER TRANSPLANTS AND EXTRACTS ON THE FORMATION OF BONE

A FURTHER EXPERIMENTAL STUDY

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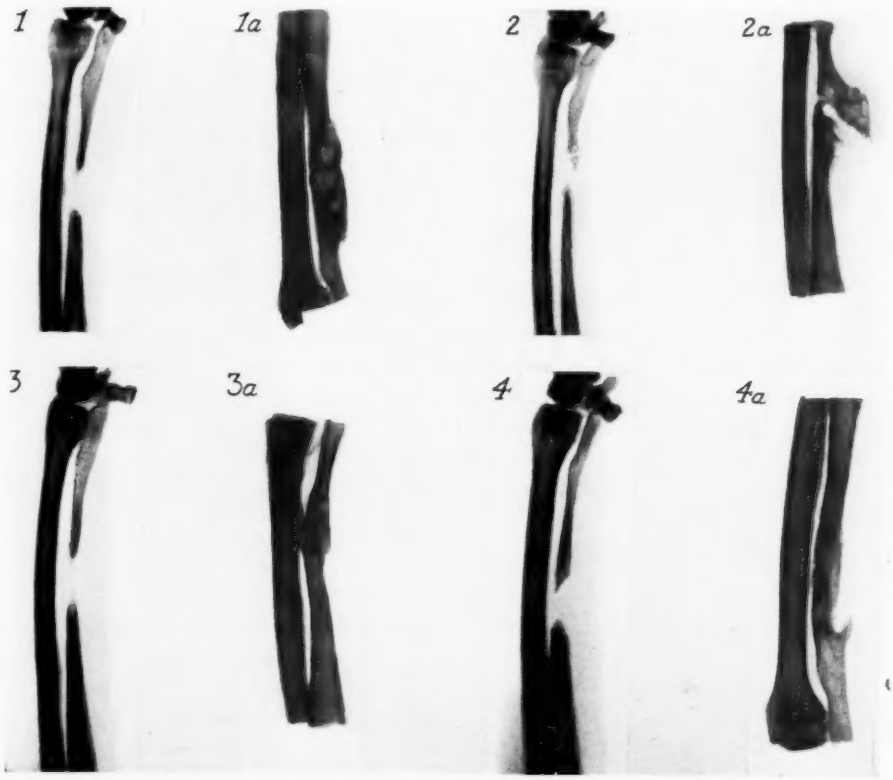
THE remarkable influences of urinary bladder transplants on the healing of defects of bone and on hyaline cartilage have been reported.[1] These studies were based on the observation of Huggins,[2] who found that the epithelium of the urinary tract of the dog after autotransplantation is capable of inducing ossification in certain connective tissues. We confirmed this observation that the newly formed bone bears an intimate relationship to the proliferating bladder epithelium and is true membranous bone with haversian canals and hematopoietic bone marrow. Our results in other experiments indicated that the presence of a growing transplant of epithelium from the urinary bladder of the dog stimulates osteogenesis and tends to cause union in defects in long bones which would ordinarily result in nonunion. In the latter experiments, defects were made in the ulnae of dogs by subperiosteal removal of a section of the shaft. At the same operation the defect in the ulna on one side was bridged by an autogenous transplant of epithelium obtained from the urinary bladder. The defect in the opposite ulna was kept as a control, and nonunion resulted in 14 of 16 controls in which the experiments lasted from one to nine months. Bone was formed in the defect containing the growing epithelium of bladder, and this formation of new bone resulted in union.

The size of our experimental defects in ulnae were probably adequate, and the evidence indicated that the new bone was formed directly under the influence of the growing bladder epithelium and was not the result of formation of bone from the periosteum bridging the defect. However, it seemed desirable to perform other experiments in which the defect was created in the bone at one operation and, after the occurrence of nonunion had unquestionably been established several months later, make the transplantation of epithelium at a second operation. The influence of the periosteum over the defect alone, and in association with bladder epithelium, was noted by this method and, also, by performing some operations in which all of the periosteum, including that along the interosseous membrane, was removed along with a long section of bone. The results obtained from these two experimental methods are herewith reported. A review of the literature on heteroplastic formation of bone has been made by Huggins.

Experimental Methods.—With the dog under ether anesthesia and using aseptic technic, the shaft of the ulna of each leg was exposed and 2 to 5 cm.

of the bone was resected subperiosteally in equal amounts on each side. The wounds in the two legs were then closed. This operative procedure was performed in six adult dogs, one of which died during the period of observation. After a lapse of time varying from 14 to 16 weeks, roentgenograms were made of the legs of the five dogs. None of the roentgenograms showed any evidence of new bone bridging the defects in either leg. In addition to nonunion, the ends of the bones at the site of the defects were found to have

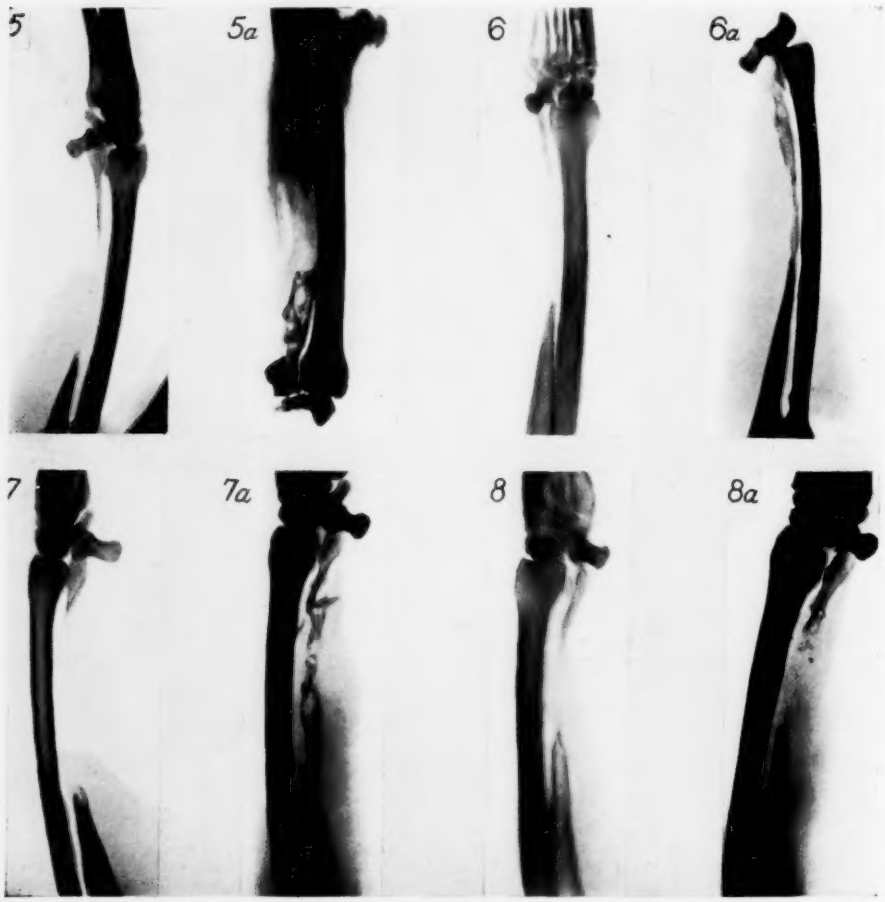


FIGS. 1, 2, 3 and 4.—Roentgenograms showing defects in the right and left ulnae of two dogs, which had been created 14 weeks previously. The periosteum was not removed with the bone.

FIGS. 1*a*, 2*a*, 3*a*, and 4*a*.—Roentgenograms made of the corresponding legs, 15 weeks after the defects in the ulnae had been bridged by autogenous transplants of bladder mucosa. The defects are filled by a mass of bone which contains numerous cysts. Firm union is present with the exception of that evidenced in 2*a*.

undergone rarefaction and had decreased in diameter. At this time, 14 to 17 weeks after creating the defects of the ulnae, the dogs were operated upon again. The healed operative wounds of the legs were opened and a condition of nonunion of bone found. The ends of the ulnae, at the site of the defect, were denuded slightly with rongeurs and a bed made in the scar tissue and periosteum for a transplant. The urinary bladder was exposed and a piece of the entire wall of the dome of the bladder was excised. The defect in the bladder and the abdominal incision were then sutured. The mucous membrane of the piece of excised bladder was then dissected from the muscularis

and was divided into two equal portions. One of these portions of mucous membrane was sutured into the defect of each ulna. The transplant was stretched from one end of the defect to the other end and was held in place by silk sutures. The wounds in the two legs were then closed in layers. The dogs were sacrificed 15 weeks later. The front legs were examined grossly, by roentgenograms, and microscopically. Specimens of blood were taken from the dogs prior to making a transplant, approximately a week after-



FIGS. 5, 6, 7 and 8.—Roentgenograms showing defects in the right and left ulnae of two dogs, which had been created 36 weeks previously. The periosteum was removed with the corresponding portion of bone. Note that the lengthy and old defects are associated with marked atrophy of the ends of the bone.

FIGS. 5*a* and 6*a*.—Roentgenograms of the corresponding legs, 108 weeks after the defects in the ulnae had been bridged by autogenous transplants of bladder mucosa.

FIGS. 7*a* and 8*a*.—Roentgenograms of the corresponding legs, 60 weeks after transplantation of bladder mucosa into the defects.

The marked increase of the amount of bone in Figures 1*a*, 2*a*, 3*a* and 4*a*, where the periosteum was not resected with the bone, over Figures 5*a*, 6*a*, 7*a* and 8*a*, where the periosteum was removed with the bone, is evident. Union was much more firm in the experiments where the periosteum was not removed.

wards, and just prior to autopsy, for determinations of the serum calcium and phosphorus.

Exactly the same operative procedures as have been described were carried out on another group of six dogs, except that when the defects were created in the ulnae the corresponding portions of periosteum were removed entirely. This group differed from the first group of dogs also, in that nine months were allowed to elapse between the time of the resection of the bone and periosteum and the transplantation of mucous membrane into the defect, and in that the dogs were permitted to live 27 months after the transplantation before being sacrificed. Two of the dogs died during the course of the experiments. One of these deaths, occurring one year after operation for transplantation, was caused from a gangrenous urinary bladder and pyelonephritis produced by a huge bladder stone. The changes in the defects were followed by occasional roentgenograms.

Results.—Gross Examination.—New bone was formed in ten of the 12 defects made in the first group of six dogs where the periosteum was not removed from the bone. The production of bone was marked and union occurred in nine out of ten defects that were bridged by new bone. The mass of new bone contained multiple cysts of various sizes similar to those that have been described. The cysts possessed epithelial lined walls and contained a brownish fluid.

Roentgenologic Examination.—Roentgenograms made at the conclusion of the experiments, 15 weeks after making the transplants, showed, with the two exceptions mentioned, that the defect was occupied by a mass of dense bone and some clear areas. The latter represent multiple cysts. The ends of the bone near the defect were no longer atrophic.

Microscopic Examination.—The defects were filled with an adult type of bone and with many cysts and masses of bladder epithelium. The cysts were lined with bladder epithelium. In general, the cysts were not so large as those found in shorter experiments. As has been noted previously, all of the newly formed bone in the defect was not immediately adjacent to bladder epithelium. Much of the new bone, however, was laid down beside the cyst walls with only a thin layer of tissue intervening. The new bone contained haversian canals and adult bone marrow. The ends of the fragments of bone at the site of the former defect were of normal appearance.

*Determinations of Blood Calcium and Phosphorus:** Analyses were made of the blood serum of this latter group of dogs just before transplantation of the bladder mucous membrane, and seven and 111 days afterwards, and, as shown in Table I, there were no significant changes in the serum calcium and phosphorus.

Interesting results were obtained in the long term experiments with the second group of dogs, in which there was removed with the segment of bone all of the corresponding periosteum. Four of the six dogs lived until the completion of the experiment.

* These studies were made in the laboratory of Dr. Alexis Hartmann.

TABLE I

DETERMINATIONS OF BLOOD CALCIUM AND PHOSPHORUS, PREOPERATIVE, AND SEVEN AND 111 DAYS POSTOPERATIVE

	Mg. of Serum Calcium			Mg. of Serum Phosphorus		
Dog No.	Before Transplant	Seven Days After	111 Days After	Before Transplant	Seven Days After	111 Days After
12	11.3	12.9	12.0	5.0	3.4	3.3
318	12.0	12.9	12.3	3.4	3.7	4.5
B2	12.0	11.8	13.5	5.6	5.1	3.8
A18	11.9	11.7	12.3	3.6	3.1	3.8
354	11.6	12.0	12.5	5.7	5.5	6.2

The defects in five of the eight ulnae were completely bridged by a tubular mass of calcified tissue containing bone cysts. Four of the defects were only partially filled. The union of the ends of the bone was firm but not solid in the specimens where the defects were entirely bridged with calcified tissue.

Roentgenologic examinations were made of the defects nine months after they were created and prior to transplantation of bladder epithelium. These films revealed long defects in the ulnae in which there was no evidence of regeneration of bone. Atrophy of the ends of the bone was indicated by their marked decrease in diameter and by rarefaction. Roentgenograms were made at intervals during the experiments and, finally, they were made at the time of the conclusion of the experiments, 15, 18 and 27 months after transplants of bladder epithelium were made to the defects in the bones. The roentgenograms revealed the ends of the bones to be connected in five of the eight specimens by a tubular-like calcified mass containing some clear spaces known to represent cysts. The defects in the other three specimens were bridged only in part. The ends of the bone had increased in diameter and in density. The new bone in general was not so dense as the old, and while it was irregular in circumference it tended to resemble cortical bone.

Microscopic Examination.—Cross-sections of the bone bridging the defects show a cyst lined by bladder epithelium surrounded completely by a ring of bone except for a sector comprising about one-eighth of the circumference. Other cysts of various sizes are adjacent. The cyst contained the remains of a granular material that failed to stain and that probably filled the cyst when it was viable. The large cyst was lined by a thin layer of atrophic bladder epithelium having occasional papillary projections into the cyst. Immediately adjacent to the thin basement layer lies a circular mass of adult bone containing numerous small cysts lined by bladder epithelium, haversian canals and small amounts of hematopoietic marrow. The bone is being formed from dense connective tissue by a process that has been described in a preceding report.[1] The connective tissue was formed between bundles of muscle fibers, after the resection of the bone and periosteum to create the experimental defect. There is no evidence that periosteum took part in the formation of the bone, and cartilage was not seen in the sections.

*Experiments, Employing Extracts of Pig's Bladder.**—In view of the striking ability of transplanted bladder epithelium, in all of our experiments, to produce calcification, we have made further attempts to isolate from this epithelium a substance capable of reproducing the same phenomena. This is an extension of previous experiments made to secure a potent extract from urinary bladder epithelium.[1]

Extractions of pig's bladders were made with water at a p_{H_2}. The extract was filtered at a p_{H_5} and salted out with sodium chloride. The aqueous extracts were adjusted to p_H's of 2, 5, and 7.5; 0.2 per cent phenol was added as a preservative. The extracts were filtered through paper and then passed through a Berkfeld filter. The total solids of the extracts varied from 2.25 to 7.78 per cent.

Alcoholic extractions were made similarly with 60 per cent alcohol. Other extracts were made without the salting-out process in order to eliminate NaCl. which might influence the results. These extracts were made by filtering and by dialyzing against tap water. A control extract was made from fresh pig's heart.

All bladder extracts were made from fresh, whole pig's bladder, as it was found impractical to remove the mucosal lining.

The intravenous injections of various dosages of these extracts did not produce any notable effects on the blood calcium and phosphorus of dogs that were attributable to the extracts directly. The frequent and continued hypodermic injections of the extracts about and into the fascia of the abdomen resulted in formation of inflammatory tissue at times, but bone was not produced in any instance. Acceleration of the union of bone was not produced by local injections of the extracts into experimental defects and fractures.

A diurnal variation in the (inorganic) serum calcium was found while making several consecutive, daily quantitative determinations of blood calcium on many normal fasting dogs for control studies. During the morning there was found consistently a rise of one to two milligrams of calcium. After reaching the peak of the rise about noon, there was a slow return of the serum calcium to normal. We have not found a reference to this observation on dogs. The phenomenon is not found in man.

COMMENT AND CONCLUSIONS

The results obtained from these experiments further amplify the fact that epithelium of the urinary bladder of the dog when transplanted has the ability of inducing ossification in certain connective tissues. The newly formed bone bears a constant and close relationship to the proliferating epithelium and as a result there is produced ossification of connective tissue through the medium of osteoblasts. This method of ossification has been used to unite the ends of a defect of long standing in the ulna of the dog.

* Supplied by the Lilly Research Laboratories. Chemical determinations made by Robert Breitenbach.

Firm union of the ends of the defects was usually produced by the osteogenic stimulus when the periosteum was not resected with the bone. When the periosteum was entirely removed with long sections of bone, it was possible to bridge the gap with true membranous bone, but firm union of the ends of the bone did not result. The newly formed bone in the defects assumed a tubular shape similar to that of normal bone and the ends of the bone were no longer atrophic under the influence of the bladder epithelium. The entire mechanism by which the proliferating bladder epithelium causes formation of bone is not known. Ossification of the defects was greatly aided by the presence of periosteum and was not preceded by the formation of cartilage. No theories are proposed to explain the mechanism of calcification. It is necessary that calcium salts be present locally in large enough quantities for utilization by osteoblasts. We have not been able to establish the action of an enzyme in the process of calcification, other than that phosphatase is known to be present in the region of ossification in a fairly high concentration. Doubtless the formation of bone under our experimental conditions will be found to be regulated by a complexity of interrelated factors acting in co-ordination similar to those concerned with the calcification of the normal skeleton.

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THE APPARENT ALTERATION OF TETANUS TOXIN WITHIN THE SPINAL CORD OF DOGS*

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IN 1935 and 1937, a series of experiments was carried out which showed that pure reflex motor tetanus (clonic spasms) can be produced without the accompaniment of the slightest degree of muscular rigidity. To demonstrate the separation of these two cardinal manifestations of tetanus, it is necessary to inject only minute quantities of tetanus toxin into an anterior horn of the dog's spinal cord. Previously Abel[1] and his coworkers had succeeded in bringing about a state of unyieldnig rigidity in the limbs of dogs by multiple intramuscular injections of tetanus toxin. They have shown that by the deposition of 1/8,000 of the ordinary lethal dose of this toxin at each of 40 different sites one can render the hind limbs of a dog rigid for three months. This observation added weight to their contention that the cause of muscular rigidity, as seen in both local and general tetanus is to be found in the action of the toxin on the voluntary muscles, and not in its action on any part of the central nervous system. To substantiate this belief we attempted the experiments referred to above. The demonstration that the effect of tetanus toxin on centers in an anterior horn of the spinal cord is the production of pure reflex motor tetanus was made in 11 dogs. The protocols of these experiments were the basis of an article which appeared in February, 1938.[2] The observations on these 11 dogs have been fully and accurately confirmed in 14 additional experiments. The present communication is not concerned with the confirmation of the preceding report, but deals with the study of an unexpected and unexplained phenomenon which occurred consistently. We refer to the observation noted in a preceding communication,[2] that every dog receiving an intraspinal injection of tetanus toxin died, although the quantity employed was a tiny fraction of the lethal dose given by any other route. In an effort to understand the cause of death following the intraspinal injection of tetanus toxin we have carried out a series of experiments that are herein reported. This study has led to the formulation of a new theory of the pathogeny of tetanus.

Before recording the actual experiments, however, it is necessary to describe the technic that has been devised for accurately depositing as little as 1/2,000 cc. at any given site. It is also desirable to make some statements concerning the dosage and the materials used in the experiments.

In all of our experimental work we have used batches of tetanus toxin prepared by Dr. Bettylee Hampil of the Sharp and Dohme laboratories. The

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details of the method of preparation will be furnished upon request. The toxin has been kept in sterile rubber-stoppered vials at 2° to 4° C. Not only has Doctor Hampil run preliminary assays of each shipment of toxin, but Dr. William Chalian, working in Dr. John J. Abel's laboratory, has repeated these preliminary assays and from time to time has reassayed each vial to detect any loss in potency. Bacteriologic studies have been made to guarantee the continued sterility of the toxins. Various dilutions of toxin, Batch No. 678, were made by Dr. John Brewer in the Department of Bacteriology. The dilutions were made with beef infusion broth, and the resulting mixtures were placed in sealed glass vials under nitrogen.

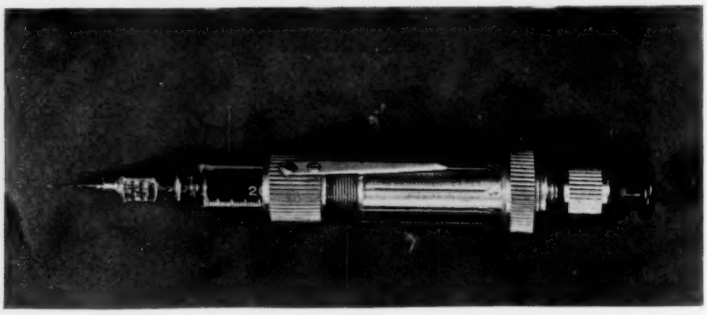

FIG. 1.—Photograph of syringe constructed in order to inject minute quantities of toxin.

Throughout our work we have adopted the dog unit described by Doctor Abel as follows: "We have found in the course of numerous experiments extending over a period of five years that injection of 480 guinea-pig LD 50's per kilogram invariably induces fatal tetanus in dogs of medium weight and age, and have arbitrarily chosen this figure as our lethal dose for dogs. This dose kills dogs taken at random in from five to nine days (when given intravenously, intramuscularly, or subcutaneously).* Neither a median nor a minimal lethal dose, but certainly larger than a statistically determined median lethal dose would be, it was adopted as a matter of convenience. We have always stated the dosage of the injected toxin in terms of standard guinea-pig units, so that our work can readily be checked by others without reference to our arbitrary dog unit."[3]

The technic for injecting minute quantities of toxin which was described in connection with our earlier spinal cord experiments was not infallible and was limited to a maximum of 0.003 cc. per injection; consequently, the apparatus illustrated in Figure 1 was devised and has been used in all animals whose number is over 104. This device† consists of a tuberculin syringe the barrel and plunger of which are held tightly by jackets of stainless steel. These jackets are threaded upon each other so that one complete turn either

* Parentheses ours.

† The authors wish to thank Dr. George Gey for his supervision of the design and construction of this instrument.

aspirates or expels 1/100 cc. Fractions of this amount are easily registered by the arm on the upper jacket which clicks at every tenth of a turn. It is entirely possible to turn the plunger accurately 1/20 of a turn, thereby delivering 1/2,000 cc. If a tuberculin syringe breaks, it is a simple matter to replace it. With this injection apparatus there may be an error of 0.0005 per 0.01 cc. because of the variations in the bore of tuberculin syringes.

EXPERIMENT 1: *Method of Procedure.*—This experiment was devised to ascertain whether or not the clonic spasms of the muscles which follow the injection of tetanus toxin into an anterior horn of a dog's spinal cord are responsible for the animal's death. To gain this knowledge a series of dogs was prepared in which toxin was placed in the distal end of the lumbar cord a few minutes after the conus and all adjacent spinal roots had been severed. By this procedure the usual evidences of reflex motor tetanus were eliminated. Postoperatively the animals had a flaccid paralysis of the hind limbs. From a study of Table I it is apparent that elimination of clonic spasms of the voluntary muscles does not prevent death following the intraspinal injection of minute quantities of tetanus toxin. Although the range of dosage given in Table I is from 1/12 to 1/50 of the ordinary lethal dose, these figures represent the maximum amount that could have been given. They do not allow for leakage and for loss of potency from exposure to the air. That this loss of potency can be as great as 50 per cent was accurately determined by assays.

Protocol of Typical Experiment.—Dog No. 15: Male, mongrel, weight 8.3 Kg. *Operation* in June 3, 1937: Under ether anesthesia, the operative field was shaved and prepared with a double application of iodine. The fifth, sixth, and seventh lumbar vertebrae were exposed and their dorsal spines and laminae removed. The operation was remarkable for the slight amount of bleeding. The conus and overlying dura were divided with scissors and the motor and sensory roots of the last three lumbar nerves on both sides were cut. The mobilized end of the cord with its surrounding dura was lifted from the spinal canal, and after all bleeding had been stopped by packing with moist gauze, a small opening was made in the ventral surface of the dura. A No. 25-gauge hypodermic needle was inserted into the central portion of the cord through this opening, and 0.003 cc. of tetanus toxin, Batch No. 670, was injected. There was no obvious leakage upon withdrawal of the needle. The wound was closed in layers with silk. The amount of toxin injected represented at the most 1/50 of a lethal dose if given intravenously.

Following the operation the dog had a flaccid paralysis of the hind limbs. There were no clonic movements of any of the muscles. The dog died at 9.30 A.M. July 5, 1937. *Autopsy* showed a few intraperitoneal adhesions. The viscera were entirely normal. The wound was clean. Specimens were taken for microscopic study.

EXPERIMENT 2: *Method of Procedure.*—The question arose whether or not injections of tetanus toxin into the white matter of the cord would be as lethal as those into the gray substance; accordingly, a group of dogs were given toxin in the region of one crossed pyramidal tract. All of the operations were performed in the lumbar region; the white fibrous band connecting the various denticulate ligaments served as a landmark for these injections. Following the laminectomy the dura was incised in the midline and the dural flap away from the operator was raised so as to expose a denticulate ligament.

This was cut to permit the cord to fall away from the dura and to facilitate rotation of the cord. Gentle upward traction on the dural flap served to bring the white line referred to above into clear view. The operator then inserted the tip of a No. 26-gauge hypodermic needle tangentially under this line. The depth of the puncture was easily controlled and in no instance was it more

TABLE I

CAUDAL PREPARATIONS

Date	Dog No.	Toxin No.	Dosage in Dog Units	Site of Injection	Symptoms and Remarks All the animals had flaccid paralysis of the hind limbs	Survival in Days	Autopsy
5/18/37....	10	30A	1/12 or less	Anterior midline	No clonic spasms	5	Grossly normal
5/27/37....	12	670	1/20 or less	Anterior right	Cord traumatized at operation	5	Hemorrhagic cystitis. Otherwise normal
6/3/37.....	15	670	1/48 or less	Anterior midline	No spasms observed	2	Grossly normal. Microscopic of cord
6/ 8/37....	16	670	1/40 or less	Anterior right	No spasms observed	2	Bladder distended with bloody urine. Slight consolidation in lungs
7/ 7/37....	22	670	1/24 or less	Anterior right	No spasms observed	2	Grossly normal
7/ 7/37....	23	670	1/33 or less	Anterior right	No spasms observed	1	Grossly normal
9/ 8/37....	40	31A	1/50 or less	Anterior midline	Injections not satisfactory. Moderate hemorrhage from puncture wound	8	Grossly normal
9/18/37....	42	31A	1/14 or less	Anterior midline	No spasms observed	2	Microscopic sections of cord. Grossly normal

An additional animal was operated upon by a student assistant. The dog became emaciated and developed ulcers over both thighs, and died on the seventeenth day. It seems fair to assume that the injection was faulty.

CONTROLS

6/ 9/37....	17	0	0	0	Operative control	30	Emaciation. Considerable vomiting before death. Autopsy negative
9/20/37....	45	31A boiled	1/13	Anterior midline	Foot injured and infected on eleventh P.O. day. Animal sacrificed on twelfth day.	12+	Infected leg and thigh.
9/21/37....	48	31A boiled	1/14	Anterior midline	Developed ulcers on thighs from pressure necrosis	16	Infected ulcers. Lungs consolidated.
9/22/37....	50	31A boiled	1/7	Anterior midline	Distemper	20	Massive consolidation of lungs. Bloody fluid in peritoneal cavity
9/30/37....	44	31A boiled	1/13	Anterior midline		5	Grossly normal

than 2 Mm. Frequently the point of the needle was so superficial that one could see a slight bulge following the deposition of the toxin solution. These injections were certainly made with greater accuracy than those aimed at the region of the anterior horn. This fact may account for the greater consistency in the results.

Eighteen animals were operated upon in this series. The amount of toxin injected ranged from 1/15 to 1/1,000 of an intravenous lethal dose. The eight dogs receiving smaller doses will be described in Experiment 6. In ten instances the dosage was approximately 1/20 of the calculated lethal dose. The physiologic alterations that ensued were the same in each of these ten animals. Death occurred with great regularity between 48 and 60 hours following the injection. No animal showed neurologic signs on the day of operation. The animals that were observed between 18 and 24 hours after the injection showed a little weakness in the right hind limb. Between 24 and 36 hours postoperatively, all of the animals showed hyperactive cutaneous and tendon reflexes in the right hind limb. In one instance gentle blowing on the foot pads would initiate a series of clonic contractions of the right hind limb but not of the left. Later all the animals showed constant muscular tremors or spontaneous clonic movements. These grew more severe until the animals were down. For a few hours before death the spasms were diminished. Not a single instance of rigidity (Starre) was observed, although in three dogs the contralateral limb was held in extension; nevertheless, in these three dogs the limbs were actively and passively flexed at all their joints. In two dogs there was a tendency to bite at the base of the tail as if the area annoyed the animal. There was not, however, any evidence of real tetanus dolorosus. One cannot draw any conclusion from this experiment because miscroscopic sections show that some of the toxin reached the anterior horn. The only advantage that white matter injections have over anterior horn injections lies in the greater accuracy with which the toxin can be placed.

EXPERIMENT 3: *Method of Procedure.*—The possibility of the upward passage of tetanus toxin in the spinal cord was commented on in the earlier report on the experimental production of reflex motor tetanus. It was pointed out that after the introduction of tetanus toxin into the lumbar cord the resultant clonic spasms are strictly limited to the site of injection. This has been found true in all subsequent lumbar injections. Surely, if this exceedingly potent toxin passed *as such* to the medullary centers by way of the spinal cord, there would be some clinical manifestation en route. Furthermore, the absence of lymphatics in the cord lessens the possibility of such a passage. The amazingly rich network of blood capillaries makes it highly improbable that any readily absorbable molecule could migrate within a cord from the lumbar region to the medulla. In order, however, to prove beyond doubt that the molecule of tetanus never reaches the vital medullary centers by moving upward in the cord, we carried out a series of experiments with transected cords, the results of which are summarized in Table II. From a study of the data assembled in this table it is clear that the introduction of

TABLE II

TOXIN INJECTED INTO DISTAL SEGMENT OF TRANSECTED CORD

Dog No.	Date of Transection	Site of Transection	Interval between Transection and Injection in Hours	Toxin No.	Dosage in Dog Units	Site of Injection	Survival Period in Days	Autopsy
33	8/ 2/37	Dorsal 7	3/4	LYO-2	1/5-	Lumbar 4—right anterior horn	7	Infection of lower incision extending down to cord
34	8/ 5/37	Dorsal 8	3/4	LYO-2	1/3-?	Lumbar 4—right posterior root	6	Infection of lower incision and of cord, which is almost severed
111	12/ 6/37	Dorsal 10	120	31A	1/4	Lumbar 2—right anterior horn	14	Grossly normal
113	12/ 7/37	Dorsal 9	96	31A	1/3	Lumbar 2—right anterior horn	7	Grossly normal
114	12/ 7/37	Dorsal 9	144	31A	1/6	Lumbar 2—linea alba	12	Pus in bladder. Otherwise normal
115	12/ 8/37	Dorsal 9	120	31A	1/5	Lumbar 2—linea alba	12	Grossly normal
116	12/ 8/37	Dorsal 9	144	31A	1/3-	Lumbar 2—linea alba	5	Bloody fluid in peritoneal cavity but no injection of peritoneal surfaces. Bladder distended with bloody fluid
117	12/ 8/37	Dorsal 9	144	31A	1/4+	Lumbar 2—linea alba	7	Grossly normal
164	1/29/38	Dorsal 6	72	678	1/20	Lumbar 3—right linea alba	9	Second incision infected. Cord slightly edematous
165	1/29/38	Dorsal 3	72	678	1/20	Lumbar 3—right linea alba	6-	Grossly normal

CONTROLS

Three controls with their cords divided in the middorsal region lived for one, two, and three months, respectively. They showed no loss of weight and were finally sacrificed. An additional animal which received one-sixth of a lethal dose of toxin showed no neurologic effects and died on the twenty-ninth day after the second operation.

tetanus toxin into the distal segment of a divided cord produces somewhat different effects from those that follow similar injections into an intact cord. The hind limbs of dogs with spinal cords divided in the middorsal region begin to jerk spontaneously within 20 hours after the introduction of tetanus toxin within the lumbar cord. At this time there is definite tactile, reflex tetanus; the slightest cutaneous stimulation serves to precipitate a series of clonic spasms of the hind limbs. The tendon reflexes are obtainable, and the effort to elicit them brings on a series of jerking, convulsive movements of the lower

half of the body. When these animals are held up by a firm grip around the thorax the hind limbs may become quiet, but when the dogs are lying down there is some spontaneous jerking. During the second 48 hours the severity and frequency of these clonic movements are increased. At the same time some stiffness is noticed in the paralyzed limbs. This stiffness is bilateral and increases in severity, occasionally giving rise to an unyielding rigidity. In most instances, however, the stiffness can be overcome by steady pressure and the limb completely flexed. Stiffness or rigidity of the affected limbs has occurred in every dog with a transected cord. Incidentally, these animals afford confirmation of the observations recorded in a previous paper.[2]

All of the animals in this experimental group were given a diet of raw beef, milk, and biscuits. In most cases this diet was eaten until the last 48 hours of life, but despite the fact that it was well taken, all of the animals lost a great deal of weight. This can be easily accounted for by the constant activity of the dogs. In one instance the loss amounted to one-fourth of the body weight in ten days. Female dogs were used so as to facilitate the passive emptying of the urinary bladder. This was done regularly.

All of the dogs with transected cords lived several days longer than those with intact cords; nevertheless, every animal died, despite careful feeding and nursing. Dogs with noninjected, transected cords have lived in this laboratory under similar conditions for many weeks without the slightest weight loss.

Autopsy of these experimental animals showed no gross changes which would explain death. It is not surprising that the action of the toxin in the distal end of a severed cord should be distinctly different from that in an intact cord. The physiologic reactions of a severed cord differ greatly from those of the intact cord. The significant fact is that all of the animals died without any apparent cause. The same observation was made on three dogs in which the dorsal cord was divided four hours after the deposition of toxin into the lumbar cord. One of these animals lived for 19 days. The frequency and severity of the clonic movements greatly diminished during the last few days of life, and it seemed as if the animal would recover. At autopsy there was evidence of a large hemorrhage into the cord at the site of injection, and this may have accounted for the diminished symptoms. The animal lost so much weight during the 19 days that it was impossible to draw any conclusions as to the cause of death.

Protocol of Typical Experiment.—Dog No. 165: Adult, female, mongrel, weight 7.2 Kg.

First Operation.—January 29, 1938, 11 A.M.: Under anesthesia, the operative field was shaved and prepared with iodine and alcohol. A laminectomy was performed on the third dorsal vertebra. The dura was not opened, but a segment of dura and spinal cord measuring 1 cm. in length was excised. The bleeding was controlled with packing. There was a gap of almost 2 cm. between the severed ends of the cord. The wound was closed with silk throughout.

January 30: There was flaccid paralysis of the hind limbs.

Second Operation.—February 1, 10 A.M.: Under ether anesthesia, the operative field was prepared as before. A laminectomy on the third lumbar vertebra was carried out.

The dura was incised in the midline and a denticulate ligament on the right side was divided. The cord was rotated so that the operator could have easy access to the lateral columns. With the special injection apparatus, 0.0026 cc. of tetanus toxin, Batch No. 678, was placed under the linea alba. There was slight oozing following the puncture. The wound was closed with silk throughout.

February 2: There is beginning jerking of the hind limbs. Tactile, reflex tetanus is present. The bladder was emptied. The dog is eating well.

February 3: Both hind limbs jerk while the animal is lying down. They are held extended but can be passively flexed; the right is stiffer than the left. The tendon reflexes can be elicited on the right but not on the left because of the constant clonic spasms. The animal feels hot. Rectal temperature 105° F. The bladder was emptied. The dog is eating and drinking.

February 4 and 5: There is no change in the animal's condition.

February 6: The animal seems sicker than yesterday.

February 7: The animal was found dead. Autopsy showed the lungs clear; no gross pathologic changes in the abdominal viscera. Both wounds were well healed. There was no sign of wound or urinary tract infection. The cord was not edematous at the point of injection.

EXPERIMENT 4: *Method of Procedure.*—Many of the animals that are included in the preceding experiments were unobserved at the time of death. In several instances, however, an effort was made to watch the manner of death, and every time that this was done it was seen that the animal would give several deep terminal gasps. The heart beat was palpable for two or more minutes after all respirations had ceased. In fact, on five occasions the chest was opened and the heart was observed to continue beating from three to five and one-half minutes after the last visible respiratory effort. This observation brought up the question whether or not paralysis of the respiratory centers accounted for the death of the animals in these experiments; accordingly, it was decided to inject minute quantities of the toxin into these centers. Fortunately, Gesell, Bricker, and Magee[4] had studied the location of the inspiratory and expiratory centers of the dog. The numerous experiments carried out by these investigators prove that the mere introduction of a sharp needle or electrode into the dog's medulla is not followed by any untoward symptoms; nevertheless, we repeated and confirmed this observation. As an added control for the deposition of tetanus toxin into so vital an organ as the medulla, we placed from 0.001 to 0.006 cc. of diphtheria toxin, boiled water, toxic serum, or filtrates from colon bacilli, meningococci, Staphylococci (H. A. strain), and typhoid bacilli (Table IV). Only with the first named substance were there any detectable effects upon the well-being or length of life of the animals. Four of the five animals receiving diphtheria toxin into the medulla died within 40 hours. The fifth, which received only 0.0005 cc. in a single injection, lived 13 days. The autopsies of the four dogs that received larger amounts of diphtheria toxin showed gross and extensive areas of hemorrhagic necrosis about the site of injection. On the fifth day there was an area of softening 2 to 3 Mm. in diameter at this site. This animal died from an acute hemorrhagic pancreatitis. It is interesting to note that diph-

theria toxin placed in the lumbar cord produces flaccid paralysis but does not cause death.

In all of the animals receiving tetanus toxin in the medulla, there was a latent period during which the dog seemed perfectly well. Even when such an enormous amount of toxin as 1/12 of a lethal dose was put into the medulla (Dog No. 175), the animal remained symptomless for seven hours. Following some of our medullary injections, the latent period has been as long as five days. It is clear that this latent period, or incubation period as it is sometimes called, is proportional to the amount of toxin injected.

The first symptom that is noticeable is difficulty in swallowing. This is soon followed by clonic spasms of the pharyngeal muscles whenever the dog attempts to eat or drink. Later these spasms occur spontaneously. The picture simulates that condition which has been described clinically as tetanohydrophobia. The spasms are not painful and between them the animals remain quiet. In no instance was there any evidence of involvement of the muscles of the trunk or limbs. The time of death varied with the quantity of toxin placed in the brain. When 1/10 of a lethal dose was injected, the animal died in about 24 hours, whereas, when 1/1,100 of a lethal amount was used, the dog lived 17 days. On the whole, it seems that death occurs a little sooner following the deposition of toxin into the medulla than into the lumbar cord, but the difference, if any, is too slight to be significant. It is certainly true that the manner of death is the same in both instances, and forms a very great contrast to the manner of death following injections of diphtheria toxin into the medulla, for in the latter group of animals there is no gasping, and the animals are comatose during the last few hours of life and die quietly.

Because of the interference with swallowing we gave glucose solutions and saline parenterally to all the animals that lived longer than 36 hours, but despite these treatments there was always great loss of weight. In the case of dogs with pharyngeal spasms living more than a week, it is impossible to say whether death is due to exhaustion, inanition, or some specific action of the toxin. The data of this experiment are summarized in Tables III and IV.

Protocol of Typical Experiment.—Dog No. 136: White and brown fox terrier, female, age nine months, weight, 5.3 Kg.

Operation.—January 5, 1938, 2.30 A.M.: Under ether anesthesia, the operative field was shaved and prepared with applications of iodine and alcohol. A dorsal midline incision was made, beginning at the inion and extending for 6 cm. The fascia was divided in the midline and the muscles were retracted. The anesthetist then flexed the animal's head to the greatest possible degree, and the dura was opened from the edge of the foramen magnum to the atlas. Great care was taken when enlarging this incision to avoid tearing into the adjacent venous sinus. After absorbing the excess cerebrospinal fluid with gauze, the operator rongeured away a small piece of the occipital bone and thus obtained good exposure of the medulla. One injection of tetanus toxin was made 2 Mm. to the right of the obex and a similar one on the left side. Each injection amounted to 0.0025 cc. of a 1/50 dilution of toxin, Batch No. 678, and was equivalent to 1/80 of an intravenous lethal dose. There was no bleeding. The wound was filled with warm normal saline and closed throughout with silk.

TABLE III

INJECTIONS OF TETANUS TOXIN INTO THE MEDULLA

Dog No.	Date	Toxin No.	Total Dosage in Dog Units	Site of Injection	Remarks	Symptoms	Survival Period in Hours	Autopsy
136.....	1/ 5/38	678	1/40	Right and left	Given fluids intraperitoneally	Pharyngeal spasms	33	Grossly normal
137.....	1/ 5/38	678	1/42	Right and left	Only fair exposure. Given fluids	Pharyngeal spasms	27	Grossly normal
138.....	1/ 6/38	678	1/42	Right and left	Delayed appearance of pharyngeal spasms	Pharyngeal spasms	60	Grossly normal
140.....	1/11/38	678	1/500	Right only	Rough dilution. Poor exposure. Given fluids intraperitoneally	Typical spasms	216	Grossly normal
142.....	1/12/38	678	1/450	Right and left	Rough dilution. Given fluids	Typical spasms	72	Grossly normal
145.....	1/12/38	678	1/10	Right and left	Fair exposure	Typical spasms	20	Sacrificed, but was moribund. Grossly normal
146.....	1/14/38	678	1/10-	Right and left	Poor exposure	Typical spasms	24	Grossly normal
148.....	1/18/38	678	1/12	Right and left	Could drink	Slight pharyngeal spasms, not typical	48	Liver large and granular
149.....	1/18/38	678	1/12	Right and left	Good exposure	Typical spasms	24	Grossly normal
166.....	2/ 2/38	678	1/1,000	Right only	? Needle came out. Could not pass stomach tube	Spasms after one week	9 days	Grossly normal
167.....	2/ 2/38	678	1/1,100	Right only	Ate beef and milk for 4 days	Spasms after 5 days	8 days	Grossly normal
175.....	2/ 7/38	678	1/12	Right and left	Poor exposure	Typical spasms. Vomiting	27	Hemorrhage in substance of medulla along needle track
176	2/ 9/38	678	1/20	Right only	Copious bleeding	Typical spasms. Turns to right	22	Grossly normal
178.....	2/10/38	678	1/23	Left only	Poor exposure	Typical spasms. Turns to left	24	Grossly normal

TABLE III (*Continued*)

Dog No.	Date	Toxin No.	Total Dosage in Dog Units	Site of Injection	Remarks	Symptoms	Survival Period in Hours	Autopsy
188.....	2/23/38	678	1/1,000	Right and left	Received fluids intraperitoneally	Typical spasms. Barking and growling	140	Liver cirrhotic. 70cc. bloody fluid in peritoneal cavity. Nothing else
189.....	2/23/38	678	1/1,100	Right and left	Eats well	Barking and growling. No symptoms	7 weeks	Sacrificed
190.....	2/23/38	678	1/2,000	Right and left	Eating until sixth day. Wants to but cannot thereafter	Occasional typical spasms	240	Questionable consolidation of lungs, probably insufficient to cause death
196.....	3/18/38	678	1/1,200	Right and left	Got distemper. Received fluids intraperitoneally	Could not eat. Had spasms after sixth day	17 days	Consolidation of lungs. Lost 30 per cent of weight
197.....	3/18/38	678	1/2,000	Right and left	Received fluids intraperitoneally	Did not eat. Had typical spasms just before death	148	Died in spasm. Some consolidation of lungs

January 5, 10 P.M.: The animal appeared quite normal.

January 6, 9 A.M.: When first seen, the animal was quiet, alert, walking about, wagging its tail. There was no trismus, no tetanus dolorosus. It gave an occasional quick jerk of the head. Frequent attempts to drink produced violent clonic spasms of the pharyngeal muscles which lasted 30 seconds. Auditory and tactile stimuli did not provoke spasms. The knee kicks were present and active, and testing them did not produce a seizure.

Twelve noon: Temperature, 107.6° F. per rectum. The dog was given 300 cc. of saline and 5 per cent glucose solution intraperitoneally. It was observed closely thereafter, until the time of death at 11.30 P.M. For the first four hours of this period, spontaneous clonic spasms of the pharyngeal muscles occurred at intervals of two to 12 minutes. The duration of each was from 15 to 30 seconds. Between the attacks the dog was quiet and in no apparent pain. At times it would shake its head and had a tendency to incline the head to the right side. It frequently scratched its right ear. The respirations became increasingly rapid. After 4 P.M. the pharyngeal spasms were interspersed with spells of jerking of the head.

At 5 P.M. another smaller injection of glucose solution was given intraperitoneally. Rectal temperature, 105° F.; pulse, 160; respirations, 84. The spasms seemed to occur at greater intervals but to last longer. The dog died at 11.30 P.M. The autopsy was negative.

EXPERIMENT 5: *Method of Procedure.*—The death of dogs under the conditions of the preceding experiments might conceivably result from a multiplication of the toxic molecule within the spinal cord and the subsequent

absorption of a fatal amount of the blood stream. Such a happening is, however, highly improbable because none of the animals showed any peripheral signs of general tetanus. To exclude the possibility of such a mechanism being at work, a number of dogs were given varying amounts of tetanus antitoxin at varying intervals after the spinal injections. It was evident from this experiment that both the amount given and the interval influence the result. A determination of the exact relationships that exist between the proportion of toxin-antitoxin and the interval between injections was not necessary for our purpose. A simpler and more exact experiment was to have the antitoxin circulating in the blood *before* the toxin was placed in the spinal cord. The results of this experiment show clearly that as much as 100 times the neutralizing dose of antitoxin can be circulating in the blood stream at the time of the spinal injection without affecting the symptoms or the time of death. This experiment shows that the death of the animals is not due to multiplication of the tetanus toxin within the spinal cord.

TABLE IV

CONTROLS FOR INTRAMEDULLARY INJECTIONS

Dog No.	Date	Material Injected	Amount Injected	Site of Injection	Remarks	Symptoms	Survival Period
118	1/ 5/38	Boiled water	0.004 cc.	Right and left		None	Indefinite
122	1/ 5/38	Boiled water	0.004 cc.	Right and left	Slight trauma to cord	None	Indefinite
124	1/ 6/38	0	0	Right and left	Inserted needle	None	Indefinite
154	1/21/38	B. *coli* toxin	0.004 cc.	Right and left	Good exposure. Distemper	None	Indefinite
155	1/21/38	Meningococcus toxin	0.004 cc.	Right and left	Good exposure. Distemper	None	Indefinite
159	1/25/38	H.A. Staphylococcus toxin	0.004 cc.	Right and left	Good exposure	None	Indefinite
162	1/27/38	B. *typhosus* toxin	0.006 cc.	Right and left	Good exposure	None	Indefinite
163	1/27/38	Meningococcus toxin	0.006 cc.	Right and left	Good exposure	None	Indefinite
179	1/12/38	Diphtheria toxin	0.006 cc.	Right and left		Not seen	20 hours
180	2/15/38	Diphtheria toxin	0.002 cc.	Right only		Cannot stand. No jerks, *etc.*	27 hours
181	2/15/38	Diphtheria toxin	0.003 cc.	Right only		Turned somersaults in cage for short period	40 hours
186	2/17/38	Diphtheria toxin	0.001 cc.	Right only		Not seen	23 hours
187	2/17/38	Diphtheria toxin	0.005 cc.	Right only		None	13 days
194	2/28/38	Toxiferous blood	0 006 cc.	Right and left		None	Indefinite

EXPERIMENT 6: *Method of Procedure.*—After establishing the fact that intraspinal injections of minute amounts of tetanus toxin cause death, we attempted to study the effects of introducing still greater dilutions of the toxin. An abstract of the data on six dogs which received intramedullary

injections of 1/1,000 or 1/2,000 of an ordinary lethal dose is given in Table IV. These dogs had clonic pharyngeal spasms and lived from six to 17 days. Because of the interference with swallowing, it is impossible to attribute their death to the action of any secondary substance. There were eight other dogs in which the toxin was put into the white matter of the lumbar cord. The first four of these dogs were given approximately 1/1,000 of a lethal dose, and except for a slight transient weakness in gait, probably due to trauma, they showed no effects from the injections. There were no significant changes in the superficial or deep reflexes, and no evidence of clonic spasms. In this respect the injections of toxin into the white matter of the lumbar cord differ from those into the medulla. This difference is probably due to the toxin reaching a larger number of motor cells following medullary injections than after lumbar injections. This experiment will have to be repeated on a larger series of animals and be combined with careful histologic studies before it can be used as an argument that tetanus toxin has no effect on the white matter of the cord. The four remaining dogs were given 1/500 of a lethal dose in the lumbar cord. Two of these showed no symptoms attributable to the toxin. The third died with typical spasms on the fourth postoperative day. The autopsy was negative. The fourth dog was most interesting. It was given two injections of 0.0025 cc. each of a 1/50 dilution of toxin, Batch No. 678, into the right side of the lumbar cord. During the next four days there were no significant symptoms. On the fifth day the right hind leg jerked constantly when the animal was standing. There was difficulty in walking. The knee kick on the left was normal but could not be tested on the right because of the constant clonic movements. The cutaneous reflexes on the right were increased. There was no stiffness. This state of tactile, reflex tetanus continued for three days, at which time the jerking gave place to tremors, which lasted four days. Thereafter the dog remained entirely well.

This animal is the only one that recovered after having unmistakable clonic spasms. It corresponds, we think, to dogs receiving from one-half to three-quarters of a lethal dose intravenously, for in these animals signs of descending tetanus develop but the dogs recover. When less than one-half of a lethal dose is given intravenously (or into the spinal fluid), no symptoms occur. It seems that the corresponding ineffective dose for lumbar injections is less than 1/500 of the intravenous dose.

Pathology.—The report of these experiments would be incomplete without some word concerning the pathologic alterations that result from the introduction of tetanus toxin into the medulla and spinal cord of dogs. Grossly, one sees only a thin blood clot along the puncture wound made by the needle. No edema has been observed nor any visible inflammatory reaction. Histologically there are definite cytologic alterations. These are best seen in the medullary specimens but are essentially the same in other parts of the cord. The alterations are surprisingly well localized to the site of injection. The adjacent cranial nerve nuclei are apparently unaffected. There is a slight polymorphonuclear infiltration about the lesion and around the neighboring

blood vessels. The needle tract is outlined by cells which seem to be microglia. The endothelium of the blood vessels is intact and there are no evidences of thrombosis. Another alteration is the presence of large numbers of phagocytic cells, apparently macrophages. The third change is in the nerve cells. Here one finds changes in the Nissl substance, which seems pale and granular. This change can be best described as chromatolysis. The nuclei of some of the cells are irregular, swollen, and distorted. A few of the nerve cells are dead; others appear viable but altered. With fiber stains one finds great alteration in the myelin, but this observation has to be interpreted with caution since the specimens were not fixed immediately upon the death of the animals. In order to really trace the sequence of cytologic alterations, a special study with the vital staining technic is now being carried out. In this an effort is being made not only to eliminate changes resulting from delayed fixation, but also to determine how much of the pathologic picture is due to trauma, how much to the presence of a foreign substance, and how much may be looked upon as the specific action of the toxin.

Discussion.—From the foregoing experiments it seems clear that tetanus toxin causes death when placed in the dog's spinal cord. This result ensues after the deposition of as little as 1/500 of the ordinary lethal dose. In several experiments we placed fractions of a lethal dose in the sciatic nerve, an anterior and a posterior nerve root, the adrenal, and the brain without any noticeable effect. This last organ was injected in six dogs. Twice the motor cortex was identified by electrical stimulation before placing the toxin in it. In not a single dog could one detect the slightest visible reaction to the toxin. This observation is in keeping with the clinical picture of tetanus, which is singularly free from cerebral symptoms. The fact that death occurs despite the introduction of the toxin into a nonvital center and despite the severance of the cord above the point of injection, points to the conclusion that tetanus toxin is altered in the spinal cord to form a new substance that is absorbed by the blood stream and causes the death of the animal. That this new substance is not susceptible to the neutralizing action of tetanus antitoxin is shown by Experiment 5, in which the presence of 100 neutralizing doses of antitoxin in the blood stream failed to prolong life.

The concept that tetanus toxin is altered in the spinal cord is not a new one. Forty years ago, Courmont and Doyon[5] suggested that central nervous system symptoms of tetanus do not appear until the toxin has been changed into a strychnine-like body. The concept that this secondary substance is a cause of death is new. In addition to the experimental data presented in this paper, there are two other observations that lend weight to the correctness of this concept. The first is the fact, well known to all investigators of the disease, that it is impossible to demonstrate the presence of tetanus toxin in the spinal cord of animals dying from tetanus, despite the preponderance of spinal cord symptoms. In commenting upon the fixation of toxin by the spinal cord after intravenous injections, Doctor Abel has recently expressed this fact by saying that "neither the bio-assay nor any other method now at

our disposal enables us to detect and assay this fixed fraction of the injected toxin."[3] It seems that the inability to detect the toxin can well be explained by its alteration.

The second fact is that tetanus antitoxin is of no avail in experimental animals receiving one or more lethal doses of toxin intravenously if it is given after central nervous symptoms appear. Abel and Chalian[6] have recently studied the length of time in which antitoxin is effective after varying amounts of toxin given intravenously. They have shown, for instance, that following three intravenous lethal doses, one can save the dog with antitoxin up until the appearance of central reflex symptoms. With larger doses there is a shorter period in which antitoxin is effective. This insusceptibility of toxin to antitoxin, once fixation and incubation have taken place, can be looked upon as additional evidence of its alteration.

SUMMARY AND CONCLUSIONS

A technic has been devised for the accurate injection of minute amounts of tetanus toxin into various parts of the dog's spinal cord. By this procedure it is possible to produce pure reflex motor tetanus without the slightest evidence of muscular rigidity. As little as 1/2,000 of an intravenous lethal dose placed in the medulla suffices to bring on reflex motor spasms of the pharyngeal muscles. The intraspinal injection of 1/400 or more of the usual intravenous lethal dose of tetanus toxin has always been followed by the death of the animal, despite the fact that the toxin was placed in a nonvital center such as the lumbar cord. The explanation that death results from an upward passage of the toxin is untenable because transection of the cord above the site of injection does not prevent death. Similarly, division of all sensory and motor pathways below the lesion is without effect. The death of the animal cannot be caused by a multiplication of the tetanus molecule and subsequent reabsorption because the presence in the circulating blood of 100 neutralizing doses of antitoxin does not prevent a fatal outcome. The tentative explanation put forward to account for the results obtained in the foregoing experiments is that tetanus toxin is altered in the spinal cord to form a secondary substance that is responsible for the dog's death.

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DISCUSSION.—DR. PETER HEINBECKER (St. Louis, Mo.): The authors, by using minute amounts of tetanus toxin injected directly into the cord, have apparently been able to separate local from clonic tetanus. This is an unusual physiologic feat. Apparently, the dosage was just adequate to bring about a facilitation for those reflexes initiated by the afferent fibers concerned in clonic reflexes, but not sufficient to facilitate appreciably the mechanism for proprioceptive reflexes concerned in local tetanus.

I am unable to accept the interpretation that local tetanus is a manifestation of alteration in the muscle itself. I adhere to the view that both local tonic and clonic tetanus are an expression of influence of the toxin on the central nervous system.

The problem of the potentiation of tetanus toxin on injection into the spinal cord is a difficult one to analyze. In 1933, Condrea and Poenaru produced evidence that tetanus toxin was modified by the diluent into which it was placed prior to injection. They found that the toxic effect increased remarkably when the toxin was united with peptone. Recently, a report has been issued by Zuger and Friedemann, in which they stated that there was a potentiation of tetanus toxin on mixing it with muscle in vitro. It is possible that such a potentiation was here also due to admixture with a substance like peptone, which increased the rapidity with which the toxin reached the vital centers. There was no evidence in any of their experiments to indicate that the amount of toxin was altered, because, in vitro, no additional antitoxin was required to neutralize the toxin mixed with peptone or muscle.

Rivers mixed tetanus toxin with spinal cord tissue and found that the amount of antitoxin required to neutralize it, in vitro, was even less than that required to neutralize the toxin alone. However, Doctor Firor informs me that after incubation, such a mixture of toxin with cord does result in a potentiation of the mixture. It is possible that in his experiments in which injections were made into the cord, slight injury resulted, and the body, acting as an incubator, permitted the development of a substance which when mixed with the toxin permitted a more rapid penetration into the vital areas than when the toxin alone was present. However, I am not certain that this is the explanation, and I feel that Doctor Firor will have to present very excellent evidence to show that a new substance has been formed, a new toxin, before the idea can be accepted.

I consider the method of action of tetanus toxin to be similar to that of strychnine on the central and peripheral nervous system. Strychnine acts by lowering the threshold for nervous excitation and it also acts by altering accommodation of the nervous system to stimuli. By that, I mean that ordinarily nerves, and presumably cells, tend to fail to respond to a prolonged stimulus after a certain period of time. We have found in our laboratory that in the presence of strychnine such a failure to respond does not occur, and I consider the activity of tetanus toxin to be very similar to that of strychnine.

I think the manner of death by tetanus to be one of exhaustion, exhaustion of the muscles from continued stimulation arising in the central nervous system. There is no evidence of a failure of the central nervous system. The muscles just tire and fail to respond. Realization of this point will guide us in our therapy. We can organize a rational form of therapy.

I have one graph which I would like to show. Some weeks ago, Doctor Firor talked to me about this subject and I told him that I could present an illustration indicating how strychnine acted upon the central nervous system, and possibly reveal how tetanus toxin acts.

Figure 1, 3A is a record of the activity of the phrenic nerve in a curarized animal. You see, there is a series of impulses coming down, then there is a

pause, and during the next respiratory effort, another series of impulses will descend. After strychnine, we get the type of activity shown in Figure 1, 3B. The central nervous system fails to accommodate and one gets long-continued activity.

When, as shown in Figure 1, 4, you record the activity in the sciatic nerve of such a curarized animal, it will be found that on very slight stimulation of the saphenous nerve, a series of responses is obtained. This would represent ordinary tactile stimulation. When the animal is stimulated a little harder, a long-continued series of responses results. It is the effect of such a continued action of the nervous system on muscles which leads to fatigue and is, in my mind, the cause of death.

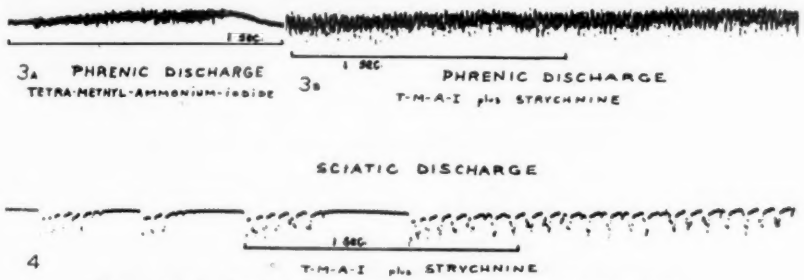

FIG. 1.—(3A) Graph showing phrenic discharge in a curarized animal.
(3B) Result on phrenic discharge after administration of strychnine.
(4) Result on sciatic discharge after administration of strychnine.

One other interesting point here—because this animal is curarized, we do not get proprioceptive impulses from the periphery, so that we have absolutely smooth intervals in our record. Such an animal, being entirely without tone, does not show the electrical evidence of proprioceptor reflexes which one obtains in the ordinary animal.

DR. WARFIELD M. FIROR (Baltimore, Md.) closing: I want to thank Doctor Heinbecker for his discussion and for his healthy incredulity. I think he is absolutely right in saying that one must offer excellent evidence before he can assume that a second toxin is formed, because this is a very unphysiologic concept—the body steps up the potency of a lethal agent for its own destruction.

I disagree, however, with Doctor Heinbecker, that fatigue is the cause of death, because in the series of animals in which we divided the conus and the lumbar nerves, there were no muscular contractions, there was no muscular activity. Nevertheless, these animals died in exactly the same manner and the same time as those that suffered from very violent muscular activity.

I am glad also that he brought up the point about the spinal cord experiments of Doctor Rivers. I may say in passing that you will note in the abstract a mention of four dogs in which tetanus toxin was injected into the lumbar cord and then, just before death, that segment of the cord was excised and injected into healthy dogs, and caused their death. We have not included that experiment in this particular communication because we have been able to obtain that result in only five out of 20 experiments, and do not think that such a proportion is statistically significant. Nevertheless, one has to explain the death of those five animals; and the experiments which we are now conducting will, I think, shed light on that point and will also offer the indisputable proof that Doctor Heinbecker wants.

BOOK REVIEW

THE HORSE AND BUGGY DOCTOR. By Arthur E. Hertzler, M.D., New York and London: Harper & Brothers, 1938.

The reviewer takes the greatest satisfaction in unequivocally praising the latest effort of Doctor Hertzler after having read the recitation of his life struggle. This biography should be read by both young and old; by the former to stimulate them to emulation and by the latter to afford them the pleasure of learning what has been accomplished by a man who has passed through certainly more than his share of vicissitudes, many of which must bring back to the reader similar situations in his own life. The book will certainly prove to be most interesting to lay people as well as to members of the medical profession. This is reflected if one consults the tabulation of the books America is reading as summarized in the weekly reviews of those most popular, in which it has risen rapidly to second place.

The author has injected a most interesting personal philosophy throughout the book, admixed with a remarkable, homely humor, at times salty, in which one can readily appreciate the reputation he has earned as a most amusing raconteur. Indeed, a little of the "Hertzlerian" humor would make anyone feel better and a continuation of it would effect a cure in a great many patients.

The almost incredible experiences through which Doctor Hertzler passed from boyhood to his present prominent position, are interestingly and fascinatingly recited, illustrating, by example, his triad for success; namely, the material, the books and *the will to do*. His progression in life is concisely indicated by the twelve chapter captions: "Medicine as It Was in My Boyhood; I Prepare to Study Medicine; I Study Medicine; I Go to the Patient; I Arrive at the Patient's Bedside; The Patient Comes to the Office; I Seek Further Education; I Educate Myself; I Practice Kitchen Surgery; I Build a Hospital; Me and My Patient; Medicine as It Is To-Day."

I do not recall ever having read a more absorbing story than that detailing his experiences in performing "kitchen surgery." It shows what can be accomplished with practically no facilities by one gifted with unusual common sense, adaptability, ingenuity, resourcefulness, determination and daring, when backed up by the preparation which the author had so laboriously acquired. The subject matter itself is most amusingly presented and the details of cases reported really thrilling.

That "a man may be known by the company he keeps" may be remarked by the friends with whom Doctor Hertzler associated himself, veritably acquiring a postgraduate education on a "shoestring." Are not the names of Jaggard, Fenner, Dean, Davis, Hans Virchow, Waldeyer, von Bergman, Fischer, Kopsch, Janzen, Lexer, Gerhardt, Jurgens, Lassar, *etc., etc.*, ones to conjure with? An imposing shelf of some thirty-odd scientific works by

Doctor Hertzler is sufficient evidence of the knowledge gained from, and the impetus given by these teachers and well exemplifies his chief desideratum, *"the will to do."*

His characterizations of operative assistants are most amusing and ironical. His conclusions relative to wound infections, as gathered from his own observations under most adverse conditions, are well worth considering seriously. They are certainly quite at variance with some of the present-day ideas. His unfortunate experiences with the establishing of a private hospital are pathetic; they will be appreciated by many of his readers who have passed through the same trials.

Thus, one could continue ad infinitum, so many are the interesting and important questions introduced by Doctor Hertzler, but one's own "Horse and Buggy" probably, it is hoped, waits.

To summarize and conclude, therefore: Read it as soon as possible, then reread much of it and find out what you missed of its context and philosophy the first time.

JAMES T. PILCHER.

BOOKS RECEIVED

THE receipt of books for review is hereby acknowledged. This statement shall be regarded as sufficient acknowledgment of the courtesy of the publishers. Selections will be made for review predicated upon the interests of the readers of the ANNALS OF SURGERY and as space permits.

THE PRACTICE OF UROLOGY. By Leon Herman, M.D. Philadelphia and London: W. B. Saunders Co., 1938.

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HUMAN PATHOLOGY. By Howard T. Karsner, M.D. 5th Ed. Philadelphia: J. B. Lippincott Co., 1938.

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